FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING MICROSPHERES OF FELODIPINE

A Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirement for the award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

Submitted by

Reg. No: 26104205

Under the guidance of

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MAY 2012

NANDHA COLLEGE OF PHARMACY AND RESEARCH INSTITUTE

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled, "**FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING MICROSPHERES OF FELODIPINE"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, was carried out by **Mr. PRAVEEN KUMAR MONDITHOKA,** Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 for the partial fulfillment for the award of degree of Master of Pharmacy in Pharmaceutics under my supervision.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

Place : Erode **Dr. (Mrs.) P.R. Radhika, M. Pharm., Ph.D.,**

Date :

DECLARATION

The work presented in this thesis entitled "FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING MICROSPHERES OF FELODIPINE**"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 under the direct supervision of Prof.**Dr.P.R.Radhika, M. Pharm., Ph.D.,** Nandha College of Pharmacy, Erode-52.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

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ACKNOWLEDGEMENT

First of all, I thank the God who is constantly showering his blessing on me. It is my great privilege pride and honor in expressing my humble thanks to my esteemed teacher and guide **Dr. (Mrs.) P. R. RADHIKA, M. Pharm, Ph.D.,** Department of Pharmaceutics, Nandha College Pharmacy, Erode for her valuable guidance, keen interest, inspiration and constant encouragement throughout the course of this investigation. Without her valuable advice and deep-rooted knowledge, this work would not have been a reality.

It is proud to express my sincere thanks to **Dr. T. Sivakumar, M. Pharm, Ph.D., Principal** Nandha College of Pharmacy, with a deep sense of gratitude for his encouragement, co-operation , kind suggestion and providing the best facilities during this work .

I express my loyal thanks to **Thiru.V.Shanmugam B.com.Chairman** and **Mr. Nandha Kumar Pradeep, M.B.A., Secretary,** Nandha College of Pharmacy, Erode for providing all the facilities to make this work a success.

I owe my warm and humble thanks to **Dr. S. Tamilzharasi,** H.O.D. Dept. of Pharmaceutics, **Mr. Jagadeeswaran,** M. Pharm., Asst Prof. Dept. of Pharm. Analysis, Prof.**Dr.Sengotuvelu,** M.Pharm. Ph.D, Dept. of Pharmacology, Prof **Dr.Duraisamy,** M.Pharm. Ph.D. Dept. of Pharmacognosy**. Mr.Raja,** M.Pharm, (Ph.D), Asst Prof. Dept. of Pharmaceutics, **Mrs.P.Amsa,** M.Pharm,(Ph.D) Asst professor, Department of pharmaceutics, for their immense help throughout the work.

I express my deepest and special thanks to my batch-mates **Mr. Sanath, Mr. Pavan, Mr. Tandava Krishna, Mr. Ravi, Mr. Sibu, Mr. Subash, Mr.Rajanish, Ms. Pavani, Ms. Reepa patel** for their kind co-operation help and encouragement throughout my Post-graduation.

With no words I express my heartful and deep gratitude to my friends **Mr. Sagar, Mr. Niranjan, Mr. Murali, Mr. Prakash, Mr. Bimal, Mr. Sudhir, Mr. Pratap, Mr. Pavan , Mr. Hemanth, and Mr. Cyril, w**ho always believed in me and stood with me in good and bad times.

I also take this opportunity to express my sincere thanks to all the teaching and non-teaching staff of Nandha College of Pharmacy for their kind cooperation and help throughout the course.

With no words I can hearties and deep gratitude to my dear friends always with me in good and bad times, special thanks to them for their friendship adherent love affection and encouragement they always showered on me. I am very thankful to my juniors who have contributed directly or indirectly during my dissertation.

The completion of this dissertation is not only to fulfillment my dreams but also the dreams of my parents who have taken lots of pain for me in completion of higher studies.

A word of thanks to all, those gentle people associate with this work directly or indirectly whose names I am unable to mention here.

Thank you to one and all ……

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LIST OF ABBREVIATIONS

BP	-	British Pharmacopoeia
ºC	-	Degree Centigrade
cc	-	Cubic centimeter
Conc.	-	Concentration
CR	-	Controlled-release
DDS	-	Drug Delivery System
FD	-	Floating duration
FLT	-	Floating Lag Time
FT-IR	-	Fourier transform Infrared
FDDS	-	Floating drug delivery system
g	-	Gram
GET	-	Gastric emptying time
GIT	-	Gastric intestinal tract
GRDDS	-	Gastro retentive drug delivery system
HCl	-	Hydrochloric acid
HPMC	-	Hydroxy propyl methyl cellulose
hr	-	Hour
ICH	-	International conference on Harmonization
IR	-	Infra red
IP	-	Indian Pharmacopeia
λ max	-	Lambda maximum
MCC	-	Microcrystalline cellulose
mg	-	Milligram
ml	-	Milliliter
mm	-	Millimeter

µg	-	Microgram
µl	-	Microliter
µg /ml	-	Microgram per milliliter
MMC	-	Migrating Myoelectric Complex
#	-	Mesh
N	-	Normality
nm	-	Nanometer
%	-	Percentage
pH	-	Hydrogen ion concentration
PhEur	-	European Pharmacopoeia
PVP	-	Poly vinyl pyrolidine
Qty	-	Quantity
RH	-	Relative humidity
RPM	-	Revolution per minute
SD	-	Standard deviation
SI	-	Swelling Index
SR	-	Sustained-release
SW	-	Swollen tablet
Tab	-	Tablet
USP NF	-	United State Pharmacopoeia National Formulary
UV	-	Ultraviolet
Vol	-	Volume

INDEX

INTRODUCTION

1.1 Microencapsulation: [1, 2]

Microencapsulation is one of the quality preservation techniques of sensitive substances and a method for production of materials with new valuable properties. Microencapsulation is process of enclosing micron sized particles in a polymeric shell. There are different techniques available for the encapsulation of drug entities. The encapsulation efficiency of the micro particle or microsphere or microcapsule depends upon different factors like concentration of the polymer, solubility of polymer in solvent, rate of solvent removal, solubility of organic solvent in water etc.

Microencapsulation is described as a process of enclosing micron sized particles of solids or droplets of liquids or gasses in an inert shell, which in turn isolates and protects them from the external environment. The product obtained by this process is called as microparticles, microcapsules, microspheres which differentiate in morphology and internal structure. When the particle size is below 1µm are known as nanoparticles, Nano capsules, Nano spheres respectively and particles having diameter between 3 – 800 µm are known as microparticles or microcapsules or microspheres. Particles larger than 1000 µm are known as macro particles.

Microparticles or microcapsules consist of two components namely core material and coat or shell material. Core material contains active ingredient while coat or shell material covers or protects the core material. Different types of materials like active pharmaceutical ingredients, proteins, peptides, volatile oils, food materials, pigments, dyes, monomers, catalysts, pesticides etc. Can be encapsulated with different types of coat or shell materials like ethyl cellulose, hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose, sodium alginate, PLGA, gelatin, polyesters, chitosans etc.

1.2 Ideal characteristics of microspheres:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide timescale.
- Biocompatibility with a controllable biodegradability.

1.3 Microencapsulation technique:

There are various techniques are available for the encapsulation of core materials. Broadly the methods are divided into two types.

1. Chemical methods
2. Physico-chemical methods
3. Physico-mechanical methods

Table No.1: Different techniques used for microencapsulation

Chemical processes	Physico - chemical processes	Physico - Mechanical process
• Interfacial polymerization • In situ polymerization • Poly condensation	• Coacervation and phase separation • Sol-gel encapsulation • Supercritical CO2 assisted microencapsulation	• Spray drying and congealing • Fluid bed coating • Pan coating • Solvent evaporation

Fluidized bed or air suspension method, coacervation and phase separation, spray drying and spray congealing, pan coating, solvent evaporation methods are widely used. Depending on the physical nature of the core substance to be encapsulated the technique used will be varied.

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Table No.2: Microencapsulation and their applicability's

Microencapsulation process	Nature of the Core material	Approximate particle size (µm)
• Air suspension	• Solids	35-5000*
• Coacervation and phase separation	• Solids and Liquids	2-5000*
• Multi orifice centrifugation	• Solids and Liquids	1-5000*
• Pan coating	• Solids	600-5000*
• Spray drying and congealing	• Solids and Liquids	600
• Solvent evaporation	• Solids and Liquids	5-5000*

*The 5000µm size is not a particle size limitation. The Methods are also applicable for macro coating

1.4 Chemical methods:

a) Interfacial polymerization (IFP) :

In this technique the capsule shell will be formed at or on the surface of the droplet or particle by polymerization of the reactive monomers. The substances used are multifunctional monomers. Generally used monomers include multifunctional isocyanates and multifunctional acid chlorides. These will be used either individually or in combination. The multifunctional monomer dissolved in liquid core material and it will be dispersed in aqueous phase containing dispersing agent. A coreactant multifunctional amine will be added to the mixture. This results in rapid polymerization at interface and generation of capsules hell takes place. A polyurea shell will be formed when isocyanate reacts with amine, polynylon or polyamide shell will be formed when acid chloride reacts with amine. When isocyanate reacts with hydroxyl containing monomer produces polyurethane shell.

b) In-situ polymerization:

Like IFP the capsule shell formation occurs because of polymerization monomers added to the encapsulation reactor. In this process no reactive agents are added to the core material, polymerization occurs exclusively in the continuous phase and on the continuous phase side of the interface formed by the dispersed core material and continuous phase. Initially a low molecular weight prepolymer will be formed, as time goes on the prepolymer grows in size, it deposits on the surface of the dispersed core material there by generating solid capsule shell. E.g. encapsulation of various water immiscible liquids with shells formed by the reaction at acidic pH of urea with formaldehyde in aqueous media. Wang Qiangbin prepared Carboxyl-functionalized magnetic microspheres by in situ polymerization of styrene and methyacrylic acid at 85°C in the presence of nano-Fe_3O_4 in styrene, using lauryl peroxide as an initiator.

1.5 Physico-chemical methods:

a) Coacervation and phase separation:

It is defined as partial desolvation of a homogeneous polymer solution into a polymer-rich phase (coacervate) and the poor polymer phase (coacervation medium). The term originated from the Latin "acervus" meaning "heap". This was the first reported process to be adapted for the industrial production of microcapsules. Currently, two methods for coacervation are available, namely simple and complex processes. The mechanism of microcapsule formation for both processes is identical, except for the way in which the phase separation is carried out. In simple coacervation a desolvation agent is added for phase separation, whereas complex coacervation involves complexation between two oppositely charged polymers. The three basic steps in complex coacervation are:

(i) formation of three immiscible phases;

(ii) deposition of the coating; and

(iii) Rigidization of the coating.

First step include formation of three immiscible phases; liquid manufacturing vehicle, core material, coating material. The core material is dispersed in a solution of the coating polymer. The coating material phase, an immiscible polymer in liquid state is formed by

(i) changing temperature of polymer solution, e.g. ethyl cellulose in cyclohexane (N-acetyl P-amino phenol as core),

(ii) addition of salt, e.g. addition of sodium sulphate solution to gelatine solution in vitamin encapsulation

(iii) addition of nonsolvent, e.g. addition of isopropyl ether to methyl ethyl ketone solution of cellulose acetate butyrate (methylscopalamine hydrobromide is core),

(iv) addition of incompatible polymer to the polymer solution, e.g. addition of polybutadiene to the solution of ethyl cellulose in toluene (methylene blue as core material),

(v) Inducing polymer – polymer interaction, e.g. interaction of gum Arabic and gelatin at their iso-electric point Second step, includes deposition of liquid polymer upon the core material. Finally, the prepared microcapsules are stabilized by crosslinking, desolvation or thermal treatment.

Crosslinking is the formation of chemical links between molecular chains to form a three-dimensional network of connected molecules. The vulcanization of rubber using elemental sulfur is an example of crosslinking, converting raw rubber from a weak plastic to a highly resilient elastomer. The strategy of covalent crosslinking is used in several other technologies of commercial and scientific interest to control and enhance the properties of the resulting polymer system or interface, such as thermosets and coatings. Crosslinking has been employed in the synthesis of ion-exchange resins and stimuli-responsive hydrogelsmade from polymer molecules containing polar groups. As polyelectrolytes, hydrogels are inherently water soluble. To make them insoluble, they are chemically cross linked during manufacture or by a second reaction following that of polymerization of the starting monomers. The degree of crosslinking, quantified in terms of the crosslink density, together with the details of the molecular structure, have a profound impact on the swelling characteristics of the cross linked system. E.g. Derivatives of ethylene glycol di(meth)acrylate like, Ethylene glycol acrylate, Di(ethylene glycol) diacrylate, Tetra(ethylene glycol) diacrylate, Ethylene glycol dimethacrylate, Di(ethylene glycol) dimethacrylate, Tri(ethylene glycol) dimethacrylate; Derivatives of methylenebisacrylamide like N,N.- Methylenebisacrylamide, N,N.- Methylenebisacrylamide, N,N.- (1,2- Dihydroxyethylene) bisacrylamide, glutaraldehyde, sodium tripolyphosphate etc.

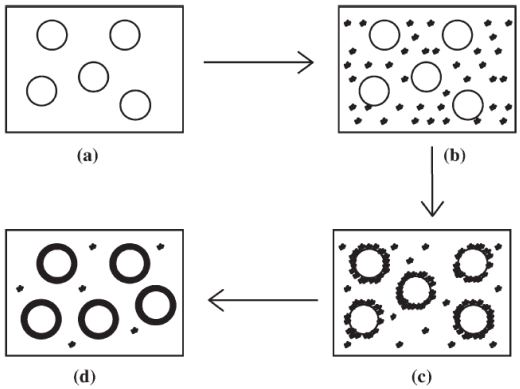


Fig. 1: Coacervation process.

(a) Core material dispersion in solution of shell polymer; (b) separation of coacervate from solution; (c) coating of core material by microdroplets of coacervate; (d) coalescence of coacervate to form continuous shell around core particles.

Xiangchun Yin prepared microspheres by Poly (styrene-alt-maleic anhydride) partially grafted with methoxy poly (ethylene glycol) (SMA-g-MPEG) was prepared by reacting poly (styrene-alt-maleic anhydride) with a sub stoichiometric amount of MPEG lithium alcoholate. Aqueous solutions of the resulting SMA-g-MPEG formed complex coacervates with poly (di allyl di methyl ammonium chloride) (PDADMAC). These phase-separated liquid polyelectrolyte complexes were subsequently cross-linked by the addition of two different polyamines to prepare cross-linked hydrogel microspheres. Chitosan served as an effective cross-linker at pH 7.0, while poly ethylenimine (PEI) was used as cross-linker under basic conditions (pH 10.5). The resulting coacervate microspheres swelled with increasing salinity, which was attributed mainly due to the shielding of the electrostatic association within the polyelectrolyte complex.

Ya-I Huang, prepared microcapsules by using gelatin and gum Arabic by coacervation. The most frequently used crosslinking agent formaldehyde in the gelatin–acacia microencapsulation process was altered by glycerol in this formulation. They found that the yield of gelatin–acacia microcapsules decreases at surfactant concentrations above or below the optimum. Inhibition of coacervation due to high concentrations of surfactants and disturbance of microencapsulation due to high hydrophilic–lipophilic balance (HLB) values have been reported. In general, the concentration of a surfactant required to increase the yield of microcapsules is too low to produce regular-sized droplets. The analysis of the size distribution shows that the microcapsules are multi-dispersed.

In the coacervation process, the pH value of a continuous gelatin phase would be adjusted above its isoelectric point to form negatively charged gelatin, which is able to create

monodispersed droplets. The positively charged gelatin is attracted to the negatively charged acacia to form coacervate droplets when the pH value is adjusted to below its isoelectric point. Therefore, the particle size distributions of emulsion droplets are effected by the factors of pH adjustment, especially the adding rate of the acidifying agent.

The report shows the indomethacin microcapsules had the slowest release rate when the coacervation pH was adjusted to the electrical equivalence pH value and not to the pH of maximum coacervate yield. Gelatin is only stable at the pH value between 4 and 6, data shown that the alkalization caused the breaking of the wall of the microcapsule made by the crosslinking agent of glycerol. Not only is the purple-colored shikonin alkalized into a blue color, but the saponification effects may also be undergone by the solvent (sesame oil) of extract containing shikonin reacting with sodium hydride.

However, this reaction would not be shown in the microcapsule made by the crosslinking agent of formaldehyde. This explains why the shell of the microcapsule made by formaldehyde is more rigid than that made by glycerol. In other words, the microcapsule made by glycerol has a more permeable shell than made by formaldehyde. The particle size of the microcapsule was not affected by the difference of crosslinking agents. Using the low concentration 3% and 6% of plasticizer glycerol instead of formaldehyde, similar morphology results were obtained. Increasing the amount of crosslinking agent leads to an increase in the encapsulation ability. However, the results indicated that above 6% of glycerin, encapsulation ability decreases as the crosslinking agent increases due to the alteration of the mechanism and inability to integrate into the network even after the addition of an excess amount.

b) Polymer Encapsulation by Rapid Expansion of Supercritical Fluids:

Supercritical fluids are highly compressed gasses that possess several advantageous properties of both liquids and gases. The most widely used being supercritical CO_2, alkanes (C_2 to C_4) and nitrous oxide (N_2O). A small change in temperature or pressure causes a large change in the density of supercritical fluids near the critical point. Supercritical CO_2 is widely used for its low critical temperature value, in addition to its nontoxic, non-flammable properties; it is also readily available, highly pure and cost-effective.

The most widely used methods are as follows:

• Rapid expansion of supercritical solution (RESS)

• Gas anti-solvent (GAS)

• Particles from gas-saturated solution (PGSS)

i) Rapid expansion of supercritical solution:

Supercritical fluid containing the active ingredient and the shell material are maintained at high pressure and then released at atmospheric pressure through a small nozzle. The sudden drop in pressure causes desolvation of the shell material, which is then deposited around the active ingredient (core) and forms a coating layer. The disadvantage of this process is that both the active ingredient and the shell material must be very soluble in supercritical fluids. In general, very few polymers with low cohesive energy densities (e.g., poly di methyl siloxanes, poly methacrylates) are soluble in supercritical fluids such as CO2. The solubility of polymers can be enhanced by using co-solvents. In some cases non solvents are used; this increases the solubility in supercritical fluids, but the shell materials do not dissolve at atmospheric pressure. Kiyoshi et al. had very recently carried out microencapsulation of TiO_2 nanoparticles with polymer by RESS using ethanol as a non-solvent for the polymer shell such as polyethylene glycol, poly(styrene)-b-(poly(methyl methacrylate)-copoly (glycidal methacrylate) copolymer (PS-b-(PMMA-co-PGMA) and poly(methyl methacrylate)

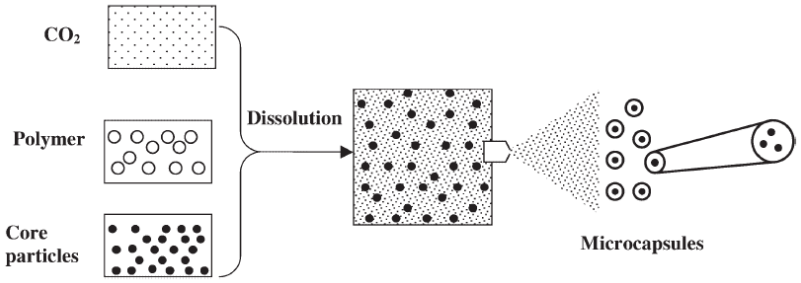


Fig. 2: Microencapsulation by rapid expansion of supercritical solutions (RESS)

ii) Gas anti-solvent (GAS) process:

This process is also called supercritical fluid anti-solvent (SAS). Here, supercritical fluid is added to a solution of shell material and the active ingredients and maintained at high pressure. This leads to a volume expansion of the solution that causes super saturation such that precipitation of the solute occurs. Thus, the solute must be soluble in the liquid solvent, but should not dissolve in the mixture of solvent and supercritical fluid. On the other hand, the liquid solvent must be miscible with the supercritical fluid. This process is unsuitable for the encapsulation of water-soluble ingredients as water has low solubility in supercritical fluids. It is also possible to produce submicron particles using this method.

iii) Particles from a gas-saturated solution (PGSS):

This process is carried out by mixing core and shell materials in supercritical fluid at high pressure. During this process supercritical fluid penetrates the shell material, causing swelling. When the mixture is heated above the glass transition temperature (Tg), the polymer liquefies. Upon releasing the pressure, the shell material is allowed to deposit onto the active ingredient. In this process, the core and shell materials may not be soluble in the supercritical fluid.

1.6 Physico-Mechanical process:

a) Spray drying and congealing :

Microencapsulation by spray-drying is a low-cost commercial process which is mostly used for the encapsulation of fragrances, oils and flavors. Core particles are dispersed in a polymer solution and sprayed into a hot chamber. The shell material solidifies onto the core particles as the solvent evaporates such that the microcapsules obtained are of polynuclear or matrix type. Chitosan microspheres cross-linked with three different cross-linking agents viz, tri poly phosphate (TPP), formaldehyde (FA) and gluteraldehyde (GA) have been prepared by spray drying technique. The influence of these cross-linking agents on the properties of spray dried chitosan microspheres was extensively investigated.

The particle size and encapsulation efficiencies of thus prepared chitosan microspheres ranged mainly between 4.1–4.7μm and 95.12–99.17%, respectively. Surface morphology, % erosion, % water uptake and drug release properties of the spray dried chitosan microspheres was remarkably influenced by the type (chemical or ionic) and extent (1 or 2%w/w) of cross-linking agents. Spray dried chitosan microspheres cross-linked with TPP exhibited higher swelling capacity, % water uptake, % erosion and drug release rate at both the cross-linking extent (1 and 2%w/w) when compared to those cross-linked with FA and GA. The sphericity and surface smoothness of the spray dried chitosan microspheres was lost when the cross-linking extent was increased from 1 to 2%w/w. Release rate of the drug from spray dried chitosan microspheres decreased when the cross-linking extent was increased from 1 to 2% w/w. The physical state of the drug in chitosan-TPP, chitosan-FA and chitosan-GA matrices was confirmed by the X-ray diffraction (XRD) study and found that the drug remains in a crystalline state even after its encapsulation. Release of the drug from chitosan-TPP, chitosan-FA and chitosan-GA matrices followed Fick's law of diffusion.

Spray congealing can be done by spray drying equipment where protective coating will be applied as a melt. Core material is dispersed in a coating material melt rather than a

coating solution. Coating solidification is accomplished by spraying the hot mixture into cool air stream. Waxes, fatty acids, and alcohols, polymers which are solids at room temperature but mutable at reasonable temperature are applicable to spray congealing. Albertini B prepared mucoadhesive microparticles and to designed innovative vaginal delivery systems for econazole nitrate (ECN) to enhance the drug antifungal activity. Seven different formulations were prepared by spray-congealing, a lipid-hydrophilic matrix was used as carrier and several mucoadhesive polymers such as chitosan, sodium carboxymethylcellulose and poloxamers were added.

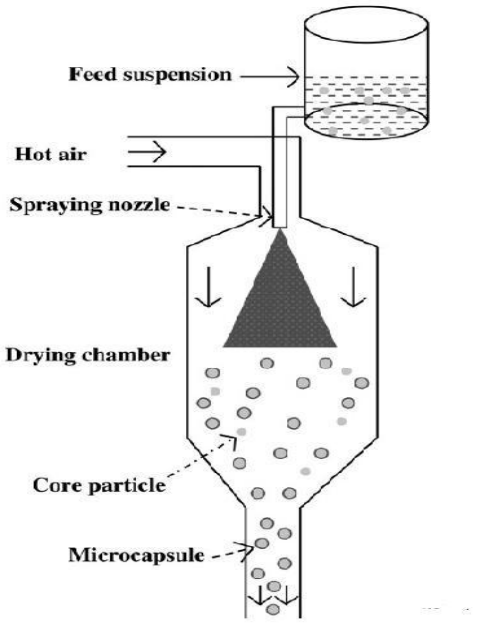


Fig. 3: Micro-encapsulation by spray-drying

b) Fluidized-Bed Technology:

The liquid coating is sprayed onto the particles and the rapid evaporation helps in the formation of an outer layer on the particles. The thickness and formulations of the coating can be obtained as desired. Different types of fluid-bed coaters include top spray, bottom spray, and tangential spray.

In the top spray system the coating material is sprayed downwards on to the fluid bed such that as the solid or porous particles move to the coating region they become encapsulated. Increased encapsulation efficiency and the prevention of cluster formation are achieved by opposing f lows of the coating materials and the particles. Dripping of the coated

particles depends on the formulation of the coating material. Top spray fluid-bed coaters produce higher yields of encapsulated particles than either bottom or tangential sprays.

The bottom spray is also known as "Wurster's coater" in recognition of its development by Prof. D.E. Wurster This technique uses a coating chamber that has a cylindrical nozzle and a perforated bottom plate. The cylindrical nozzle is used for spraying the coating material. As the particles move upwards through the perforated bottom plate and pass the nozzle area, they are encapsulated by the coating material. The coating material adheres to the particle surface by evaporation of the solvent or cooling of the encapsulated particle. This process is continued until the desired thickness and weight is obtained. Although it is a time consuming process, the multilayer coating procedure helps in reducing particle defects.

The tangential spray consists of a rotating disc at the bottom of the coating chamber, with the same diameter as the chamber. During the process the disc is raised to create a gap between the edge of the chamber and the disc. The tangential nozzle is placed above the rotating disc through which the coating material is released. The particles move through the gap into the spraying zone and are encapsulated. As they travel a minimum distance there is a higher yield of encapsulated particles.

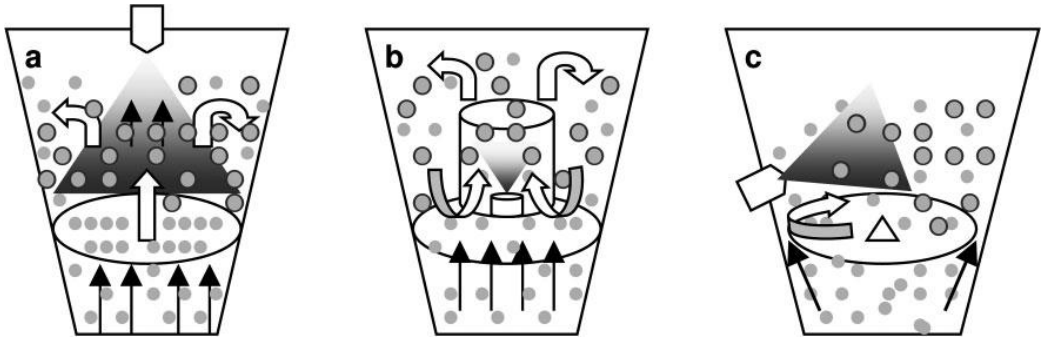


Fig. 4: Schematics of a fluid-bed coater.

(a) Top spray; (b) bottom spray; (c) tangential spray

c) Solvent evaporation:

The coating material is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be encapsulated to be dissolved or dispersed in the coating polymer solution. This mixture is added to the liquid manufacturing vehicle phase with agitation, the mixture is heated to evaporate the solvent for polymer. Here the coat material shrinks around the core material and encapsulate the core. Microspheres of 5-fluorouracil have been prepared, using three grades of ethyl cellulose as wall forming materials, and utilizing a solvent evaporation technique under ambient conditions. An alcoholic solution of 5-fluorouracil and polymer was dispersed in liquid paraffin containing

33.3 per cent *n*-heptane. The effect of stirring rate, time of stirring, drug loading, and polymer grade on drug release in two different media was evaluated. The drug loaded particles were spherical in shape and had a diameter range of 25-200 mm and were suitable for incorporating into a gel base. Drug release studies in aqueous media, showed that acidic media provide a faster release rate than neutral media. The drug release study from an aqueous gel base preparation at pH 7.0 through a synthetic membrane was found to be promising for formulation of a gel-microsphere product for the treatment of skin lesions.

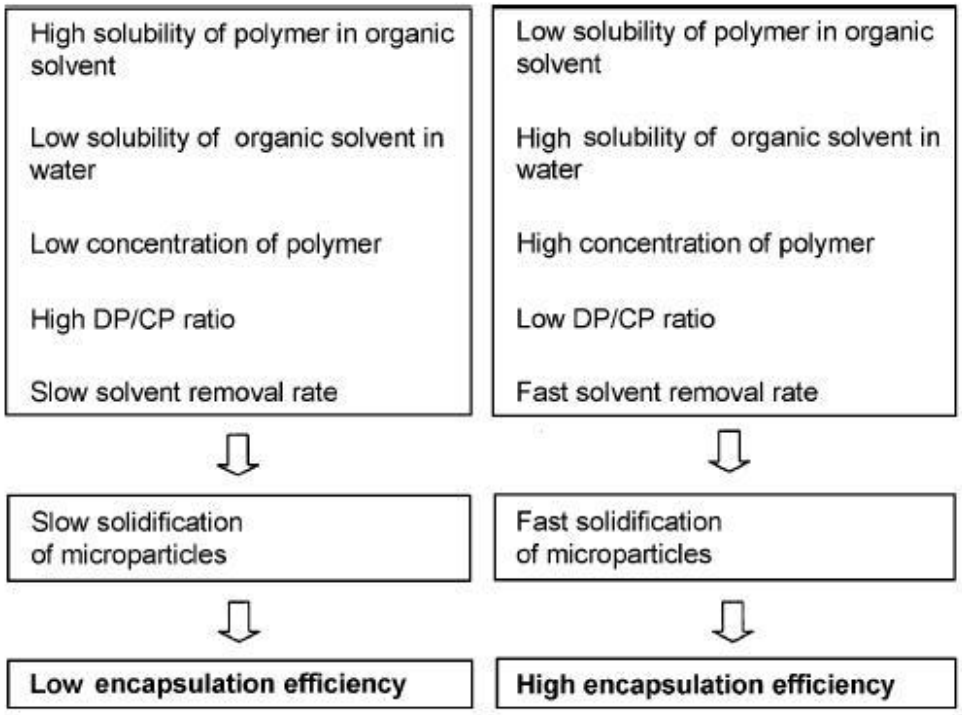
Pseudoephedrine HCl, a highly water-soluble drug, was entrapped within poly (methyl methacrylate) microspheres by a water/oil/water emulsification-solvent evaporation method. An aqueous drug solution was emulsified into a solution of the polymer in methylene chloride, followed by emulsification of this primary emulsion into an external aqueous phase to form a water/oil/water emulsion. The middle organic phase separated the internal drug-containing aqueous phase from the continuous phase. Microspheres were formed after solvent evaporation and polymer precipitation. The drug content of the microspheres increased with increasing theoretical drug loading, increasing amounts of organic solvent, polymer and polymeric stabilizer, and decreased with increasing stirring time, increasing pH of the continuous phase and increased volume of the internal and external aqueous phase.

c) Pan coating:

The coating solution is applied as atomized spray to the solid core material in the coating pan. To remove the coating solvent warm air is passed over the coated material. By using this technique larger sized particles will be coated effectively.

1.7 FACTORS INFLUENCING ENCAPSULATION EFFICIENCY:

The encapsulation efficiency of the microparticle or microcapsule or microsphere will be affected by different parameters. .



- **Solubility of polymer in the organic solvent:**

The effect of solubilities of the polymers of different PLGAs in methylene chloride was compared by measuring the methanol cloud point (Cs): Higher Cs meant that the polymer was more soluble in methylene chloride and, thus, required a greater amount of methanol to precipitate from the polymer solution. The PLGA polymer of a relatively high L/G ratio (75/25) had a higher solubility in methylene chloride than the other PLGA (L/G ratio=50/50). A lower molecular weight polymer had a higher solubility in methylene chloride than a higher molecular weight polymer. End-capped polymers, which were more hydrophobic than non-end-capped polymers of the same molecular weight and component ratio, were more soluble in methylene chloride.

Diffusion of drugs into the continuous phase mostly occurred during the first 10 minutes of emulsification; therefore, as the time the polymer phase stayed in the non-solidified (semi-solid) state was extended, encapsulation efficiency became relatively low. In Mehta's study, polymers having relatively high solubility in methylene chloride took longer to solidify and resulted in low encapsulation efficiencies, and vice versa. Particle size and bulk density also varied according to the polymer. Since polymers having higher solubilities in methylene

chloride stayed longer in the semi-solid state, the dispersed phase became more concentrated before it completely solidified, resulting in denser micro particles.

The use of relatively hydrophilic PLGA which carried free carboxylic end groups resulted in significantly higher encapsulation efficiency compared to that of an end-capped polymer. A similar explanation as above applies to this observation: Hydrophilic PLGA is relatively less soluble in the solvent, methylene chloride, and precipitates more quickly than the end-capped one. High solidification rate might have increased the encapsulation efficiency. On the other hand, the authors attribute the increase to the enhanced interaction between PLGA and the protein through hydrogen bonding and polar interactions. Walter. Also observed an increased encapsulation efficiency from using relatively hydrophilic PLGA in DNA micro encapsulation. The hydrophilicity of the polymer enhanced the stability of the primary emulsion, and it contributed to such an increase was due to the slow solidification of the microparticles.

- **Solubility of organic solvent in water:**

Methylene chloride resulted in higher encapsulation efficiency as compared with chloroform or benzene, even though methylene chloride was a better solvent for poly (lactic acid) (PLA) than the others. Methylene chloride is more soluble in water than chloroform or benzene. The 'high' solubility allowed relatively fast mass-transfer between the dispersed and the continuous phases and led to fast precipitation of the polymer. The significance of solubility of the organic solvent in water was also confirmed by the fact that the addition of water-miscible co-solvents such as acetone, methanol, ethyl acetate, or dimethyl sulfoxide (DMSO), contributed to increase of the encapsulation efficiency. Knowing that the methanol is a non-solvent for PLA and a water-miscible solvent, it can be assumed that methanol played a dual function in facilitating the polymer precipitation: First, the presence of methanol in the dispersed phase decreased the polymer solubility in the dispersed phase. Second, as a water-miscible solvent, methanol facilitated diffusion of water into the dispersed phase.

The low encapsulation efficiency of benzene is explained such that benzene required a larger amount of water (non-solvent) than methylene chloride for precipitation of the polymer, and the drug was lost due to the delayed solidification. However, given that benzene is a poorer solvent than methylene chloride for a PLA polymer, this argument does not agree with the widely spread idea that a poor solvent requires a smaller amount of non-solvent to precipitate a polymer. In fact, there could have been a better explanation if they had

considered that the delayed solidification was due to the low solubility of benzene in water: As a poor solvent for a PLA polymer, benzene requires only a small amount of non-solvent for complete solidification of the polymer. However, since benzene can dissolve only a tiny fraction of water, it takes much longer to uptake water into the dispersed phase. That is, while solubility of a polymer in an organic solvent governs the quantity of a nonsolvent required in precipitating a polymer, solubility of the organic solvent in the non-solvent limits diffusion of the non-solvent into the polymer phase. Thus, when a cosolvent system is involved, both solubility of a polymer in a solvent and solubility of the solvent in a non-solvent participate in determining the solidification rate of the dispersed phase.

Lysozyme-loaded PLGA microparticles were prepared using the oil in water (o/w) single emulsion technique. Here, the authors used a co-solvent system, varying the ratio of the component solvents. DMSO was used for solubilization of lysozyme and PLGA, and methylene chloride was used for generation of emulsion drops as well as solubilization of PLGA. Encapsulation efficiency increased, and initial burst decreased as the volume fraction of DMSO in the co-solvent system increased. Particle size increased, and density of the microparticle matrix decreased with increasing DMSO. Overall, these results indicate that the presence of DMSO increased the hydrophilicity of the solvent system and allowed fast extraction of the solvent into the continuous phase, which led to higher encapsulation efficiency and larger particle size.

- **Concentration of the polymer:**

Encapsulation efficiency increases with increasing polymer concentration. For example, the encapsulation efficiency increased from 53.1 to 70.9% when concentration of the polymer increased from 20.0 to 32.5% (Mehta et al. High viscosity and fast solidification of the dispersed phase contributed to reducing porosity of the micro particles as well. The contribution of a high polymer concentration to the encapsulation efficiency can be interpreted in two ways. First, when highly concentrated, the polymer precipitates faster on the surface of the dispersed phase and prevents drug diffusion across the phase boundary. The high concentration increases viscosity of the solution and delays the drug diffusion within the polymer droplets.

Encapsulation efficiency and particle size increase as the volume of the continuous phase increases. For example, the encapsulation efficiency increased more than twice as the ratio of the dispersed phase to the continuous phase (DP/CP ratio) decreased from 1/50 to 1/300. It is likely that a large volume of continuous phase provides a high concentration gradient of the

organic solvent across the phase boundary by diluting the solvent, leading to fast solidification of the microparticles.

A relevant observation is described in the literature (Sah,. In this example, which utilized ethyl acetate as a solvent, the formation of microparticles was dependent on the volume of the continuous phase. When 8 mL of PLGA solution (o) was poured into 20 or 50 mL of water phase (w), the polymer solution was well disintegrated into dispersed droplets. On the other hand, when the continuous phase was 80 mL or more, the microspheres hardened quickly and formed irregular precipitates. This is because the large volume of continuous phase provided nearly a sink condition for ethyl acetate and extracted the solvent instantly. Due to the fast solidification of the polymer, particle size increased with increasing volume of the continuous phase. Microparticles generated from a low DP/CP ratio had a lower bulk density (0.561 g/cc at 1/50 vs. 0.357 g/cc at 1/ 300), which the authors interpret as an indication of higher porosity of the polymer matrix (Mehta et al., On the other hand, a different example shows that a higher DP/ CP ratio resulted in increased porosity, providing a large specific surface area (measured by the BET method) and the scanning electron microscope (SEM) pictures as evidence .

This apparent discrepancy can be explained by the fact that low bulk density (Mehta et al., is not a true reflection of porosity but a result of large particle size. In fact, porosity increases with increasing DP/CP ratio, i.e., decreasing rate of the polymer precipitation.

- **Rate of solvent removal:**

The method and rate of solvent removal influence the solidification rate of the dispersed phase as well as morphology of the resulting microparticles. In the emulsion-solvent evaporation or extraction method, the solvent can be removed by

(i) Evaporation, in which the solvent is evaporated around its boiling point or

(ii) Extraction into the continuous phase.

The rate of solvent removal can be controlled by the temperature ramp or the evaporation temperature in the former and by the volume of the dilution medium in the latter. PLGA microparticles containing salmon calcitonin (SCT) were prepared by emulsification, followed by different solvent removal processes. In the temperature dependent solvent removal process, the solvent (methylene chloride) was removed by increasing the temperature from 15 to 40^{o}C at different rates. The microparticles that resulted from this process had a hollow core and a porous wall.

The core size and wall thickness were dependent on the temperature ramp. A rapid rise in temperature resulted in a thin wall and a large hollow core, whereas a stepwise temperature rise (15 to 25, then to 40^{o}C) resulted in a reduced core size. It is believed that the hollow core was due to the rapid expansion of methylene chloride chloride entrapped within the solidified microparticles. In controlled extraction of the solvent, the solvent was removed gradually and slowly by dilution of the continuous phase, which left the microparticles in the soft state for a longer period of time.

The resulting microparticles showed a highly porous honeycomb- like internal structure without a hollow core. In the later study, it was noted that the porosity was a function of the amount of water diffused into the dispersed phase from the continuous phase, which could only be allowed before the dispersed phase solidified completely .In other words, the high porosity of the microparticles that fast polymer solidification results in high encapsulation efficiency, this does not apply to the observation of Yang *et al.*. Here, the encapsulation efficiency was not affected by the solvent evaporation temperature. It may be due to the different processing temperatures influenced not only the rate of polymer solidification but also the diffusivity of the protein and its solubility in water. While the high temperature facilitated solidification of the dispersed phase, it enhanced diffusion of the protein into the continuous phase, compromising the positive effect from the fast solidification.

- **Interaction between drug and polymer:**

Interaction between protein and polymer contributes to increasing encapsulation efficiency. Generally, proteins are capable of ionic interactions and are better encapsulated within polymers that carry free carboxylic end groups than the end-capped polymers. On the other hand, if hydrophobic interaction is a dominant force between the protein and the polymer, relatively hydrophobic end-capped polymers are more advantageous in increasing encapsulation efficiency. For example, encapsulation efficiencies of more than 60% were achieved for salmon calcitonin (SCT) microparticles despite the high solubility of SCT in the continuous phase. This is attributed to the strong affinity of SCT to hydrophobic polymers such as PLGA. On the other hand, such interactions between protein and polymer can limit protein release from the microparticles. In certain cases, a co-encapsulated excipient can mediate the interaction between protein and polymer.

Encapsulation efficiency increased when gamma hydroxyl propyl cyclo sdextrin (g-HPCD) were co-encapsulated with tetanus toxoid in PLGA microparticles. It is supposed that the g-HPCD increased the interaction by accommodating amino acid side groups of the

toxoid into its cavity and simultaneously interacting with PLGA through van der Waals and hydrogen bonding forces.

- **Solubility of drug in continuous phase:**

Drug loss into the continuous phase occurs while the dispersed phase stays in a transitional, semi-solid state. If the solubility of the drug in the continuous phase is higher than in the dispersed phase, the drug will easily diffuse into the continuous phase during this stage. For example, the encapsulation efficiency of quinidine sulfate was 40 times higher in the alkaline continuous phase (pH 12, in which quinidine sulfate is insoluble) than in the neutral continuous phase (pH 7, in which quinidine sulfate is very soluble)

- **Molecular weight of the polymer:**

The effect of molecular weight of the polymer on encapsulation efficiency developed a long-acting injectable huperzine A-PLGA microsphere for the chronic therapy of Alzheimer's disease, the microsphere was prepared by using o/w emulsion solvent extraction evaporation method. The morphology of the microspheres was observed by scanning electron microscopy. The distribution of the drug within microspheres was observed by a confocal laser scanning microscope.

The results indicated that the PLGA 15000 microspheres possessed a smooth and round appearance with average particle size of 50 μm or so. The encapsulation percentages of microspheres prepared from PLGA 15 000, 20 000 and 30 000 were 62.75, 27.52 and 16.63%, respectively. The drug release percentage during the first day decreased from 22.52% of PLGA 30 000 microspheres to 3.97% of PLGA 15a000 microspheres, the complete release could be prolonged to 3 weeks. The initial burst release of microspheres with higher molecular weight PLGA could be explained by the inhomogeneous distribution of drug within microspheres. The encapsulation efficiency of the microspheres improved as the polymer concentration increase in oil phase and PVA concentration decreased in aqueous phase. The burst release could be controlled by reducing the polymer concentration. Evaporation temperature had a large effect on the drug release profiles. It had better be controlled under 30°C. Within a certain range of particle size, encapsulation efficiency decreased and drug release rate increased with the reducing of the particle size.

1.8 Applications:

The technology has been used widely in the design of controlled release and sustained release dosage forms.

- To mask the bitter taste of drugs like Paracetamol, Nitrofurantoinetc.

- To reduce gastric and other G.I. tract irritations.
- Sustained release Aspirin preparations have been reported to cause significantly less G.I. bleeding than conventional preparations.
- A liquid can be converted to a pseudo-solid for easy handling and storage. eg.Eprazinone.
- Hygroscopic properties of core materials may be reduced by microencapsulation eg. Sodium chloride.
- Carbon tetra chlorides and a number of other substances have been microencapsulated to reduce their odor and volatility.
- Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g. Vit-A, Palmitate.

1.9 Advantages:

- Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
- Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
- Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour.
- The size, surface charge and surface hydrophillicity of microspheres have been found to be important in determining the fate of particles in vivo.

1.10 Floating systems: [3, 4, 5. 6. 7]

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.

1.11 Types of FDDS: [4, 5, 26]

Based on mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are effervescent system and non-effervescent system

A. Effervescent system:

Effervescent system include use of gas generating agents, carbonate(sodium bicarbonate) and other organic acids (citric acid and tartaric acid) to produce carbon dioxide(CO_2) gas, thus

reducing the density of the system and making it to float on the gastric fluid. The effervescent further classified into two types.

(I) Gas Generating Systems:

1. Intra Gastric Single Layer Floating Tablet

These are formulated by the CO_2 generating agents and the drug within matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach and this leads to increase in GRT and better control over fluctuations in plasma drug concentration.

2. Intra Gastric Bilayered Floating Tablets:

These are also compressed tablets and contain two layers for:

Immediate release layer and Sustained release layer

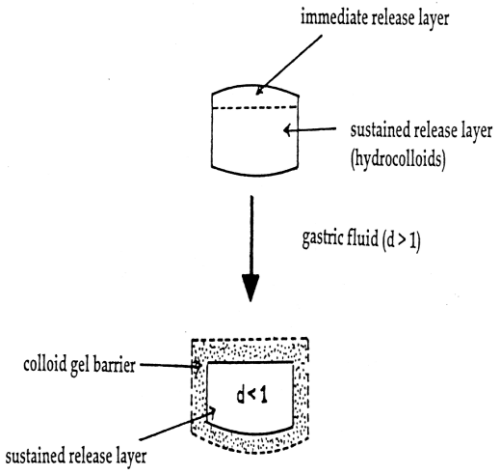


Fig. 5: Intra Gastric Bilayered Floating Tablets

3. Multiple Unit type floating pills

These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature it sinks at once and then forms swallowing pills like balloon and float as the density decreases

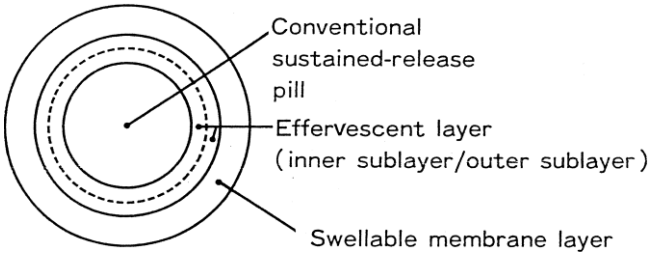
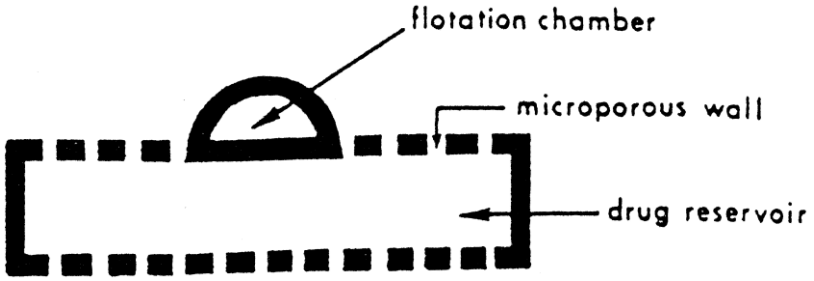


Fig. 6: A multiple-unit oral floating dosage system

II. Volatile liquid/ vacuum containing systems:

1. Intragastric Floating Gastroretentive Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment



Intragastric

Fig. 7: floating drug delivery device

2. Inflatable Gastroretentive Delivery System:

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, impregnated polymeric matrix, and then encapsulated in a gelatin capsule. After oral administration of the capsule dissolve to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid.

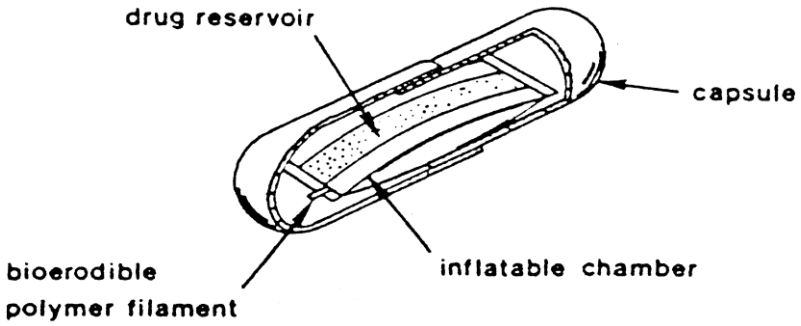


Fig. 8: Gastro-inflatable drug delivery

3. Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is Impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the Semi permeable membrane into osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in Solution form through the delivery orifice

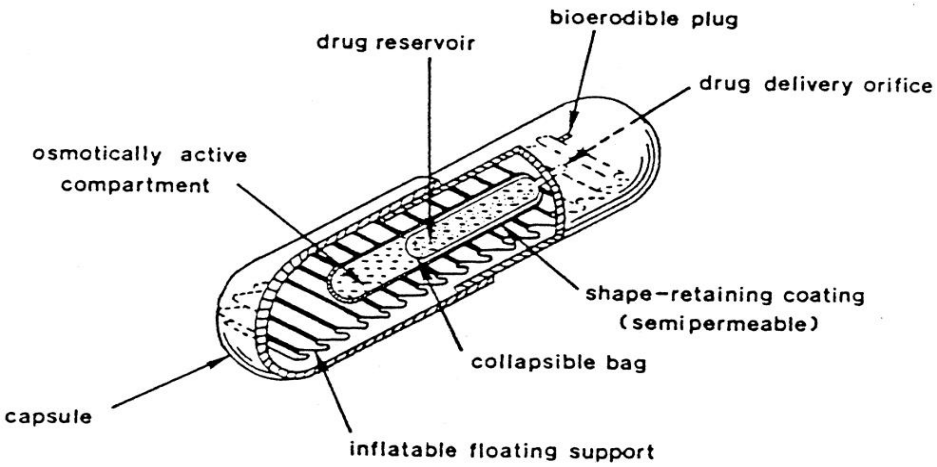


Fig. 9: Intragastric osmotic controlled drug delivery system

B. Non Effervescent Systems:

The non effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethaacrylates, polystyrenes etc .

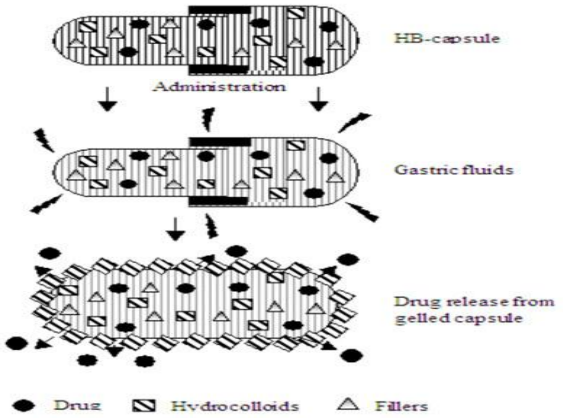


Fig. 10: Principle of hydro dynamically balanced system

The various types of systems are:

• Single Layer Floating Tablets:

They are formed by intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

- **Alginate Beads:**

Multi unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5mm diameter can be prepared by dropping sodium alginate into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hr. These floating beads gave a prolonged residence time of more than 5.5 hr.

Hollow Microspheres:

Multiple-unit hollow microspheres by emulsion solvent diffusion technique were prepared with drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Microballons were floatable in vitro for 12 hours when immersed in aqueous media. Radio graphical studies proved that microballons orally administered to humans were dispersed in the upper part of the stomach and retained there for 3 hours against peristaltic movement

1.12 Advantages and Disadvantages of FDDS

Advantages of FDDS:

- Drugs that act locally in the stomach e.g. antacids, antibiotics for microbial based ulcer, etc.
- Drugs that are absorbed primarily in the stomach e.g. Albuterol
- Drugs those are poorly soluble in alkaline pH.
- Drugs that have narrow absorption window for absorption of the drugs which are absorbed from the proximal part of the small intestine. E.g. riboflavin, Levodopa, PABA. Drugs that degrade in colon e.g. Captopril, Metoprolol

Disadvantages of FDDS:

- High variability in gastric emptying time due to variations in emptying process.
- Drugs that cause irritation and leisions to gastric mucosa and unstable in gastric fluid cannot be formulated as FDDS
- Drugs with unpredictable bioavailability, minimum effective concentration are achieved slowly.

1.13 INTRODUCTION TO HYPERTENSION [8, 9]

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is also referred to as **high blood pressure** or shortened to **HT**, **HTN** or **HPN**. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either **essential** (primary) or **secondary**. Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure. It is common. About 90-95% of hypertension is essential hypertension. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma).

Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated Beginning at a systolic pressure (which is peak pressure in the arteries, which occurs near the end of the cardiac cycle when the ventricles are contracting) of 115 mmHg and diastolic pressure (which is minimum pressure in the arteries, which occurs near the beginning of the cardiac cycle when the ventricles are filled with blood) of 75 mmHg (commonly written as 115/75 mmHg), cardiovascular disease (CVD) risk doubles for each increment of 20/10 mmHg.

1.14 Classification:

A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is a common occurrence among the elderly. These readings are based on the average of seated blood pressure readings that were properly measured during 2 or more office visits. In individuals older than 50 years, hypertension is considered to be present when a person's blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with blood pressures over 130/80 mmHg along with Type 1 or Type 2 diabetes or kidney disease require further treatment.

Table: 3 Classification of Hypertension

Classification	Systolic pressure		Diastolic pressure	
	mmHg	kPa (kN/m^2)	mmHg	kPa (kN/m^2)
Normal	90–119	12–15.9	60–79	8.0–10.5
Prehypertension	120–139	16.0–18.5	80–89	10.7–11.9
Stage 1	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2	≥160	≥21.3	≥100	≥13.3
Isolated systolic hypertension	≥140	≥18.7	<90	<12.0

Resistant hypertension is defined as the failure to reduce blood pressure to the appropriate level after taking a three-drug regimen (include thiazide diuretic). Guidelines for treating resistant hypertension have been published in the UK and US.

Excessive elevation in blood pressure during exercise is called exercise hypertension. The upper normal systolic values during exercise reach levels between 200 and 230 mm Hg. Exercise hypertension may be regarded as a precursor to established hypertension at rest.

1.15 Signs and Symptoms:

Mild to moderate essential hypertension is usually asymptomatic. Accelerated hypertension is associate with headache; somnolence, visual disturbances, nausea and vomiting (hypertensive encephalopathy).Retinas are affected with narrowing of arterial diameter to less than 50% of venous diameter,copper or silver wire appearance, exudates, hemorrhages, or papilledema. Some signs and symptoms are especially important in infants and neonates such as failure to thrive, seizure, irritability or lethargy, and respiratory distress. While in children hypertension may cause headache, fatigue, blurred vision, epistaxis, and bell palsy.

Some signs and symptoms are especially important in suggesting a secondary medical cause of chronic hypertension, such as centripetal obesity, "buffalo hump," and/or wide purple abdominal striae and maybe a recent onset of diabetes suggest glucocorticoid excess either due to Cushing's syndrome or other cause. Hypertension due to other secondary endocrine diseases such as hyperthyroidism, hypothyroidism, or growth hormone excess show symptoms specific to these disease such as in hyperthyrodism there may be weight loss, tremor, tachycardia or atrial arrhythmia, palmar erythema and sweating. Signs and symptoms associated with growth hormone excess such as coarsening off acialfeatures, prognathism, macroglossia, , hyperpigmentation, and hyperhidrosis may occur in these patients. Other endocrine causes such as hyper aldosteronism may cause less specific symptoms such as numbness, polyuria, polydipsia, hypernatraemia and metabolic alkalosis. A systolic bruit heard over the abdomen or in the flanks suggests renal artery stenosis. Also radio femoral delay or diminished pulses in lower versus upper extremities suggests coarctation of the aorta.

Hypertension in patients with pheochromocytomas is usually sustained but may be episodic. The typical attack lasts from minutes to hours and is associated with headache, anxiety, palpitation, profuse perspiration, pallor, tremor, and nausea and vomiting. Blood pressure is markedly elevated, and angina or acute pulmonary edema may occur. In primary aldosteronism, patients may have muscular weakness, polyuria, and nocturia due to hypokalemia. Chronic hypertension often leads to left ventricular hypertrophy, which can present with exertional and paroxysmal nocturnal dyspnea. Cerebral involvement causes stroke due to thrombosis or hemorrhage from microaneurysms of small penetrating intracranial arteries. Hypertensive encephalopathy is probably caused by acute capillary congestion and exudation with cerebral edema, which is reversible.

Signs and symptoms associated with pre-eclampsia and eclampsia can be proteinuria, edema, and hallmark of eclampsia which is convulsions, other cerebral signs may precede the convulsion such as nausea, vomiting, headaches, and blindness.

2. REVIEW OF LITERATURE

Josephine LJ, *et al.*[10], The purpose of the research work was to prepare and evaluate the floating microspheres of stavudine as a model drug for prolongation of gastric retention time for oral delivery. Stavudine is a synthetic analog of reverse transcriptase inhibitor with short half-life (0.8 to 1.5hr). The floating microspheres of Stavudine were prepared by emulsion solvent diffusion method using Eudragit RS 100 as a rate controlling polymer. The floating microspheres were evaluated for micromeritic properties, particle size, % yield, *in vitro* buoyancy, incorporation efficiency and drug release. The size or average diameter of prepared microspheres were recognized and characterized by scanning electron microscopic methods. The prepared microspheres were found to be spherical and free flowing and remain buoyant for more than 12 hrs. The drug-loaded microspheres (A1) showed encapsulation efficiencies up to 88% and also showed good micromeritic properties for their suitability as oral dosage forms. The microspheres having lower densities exhibited good buoyancy effect and hence, these could be retained in the gastric environment for more than12 h. Thus, the present formulations would be capable of reducing the frequency of administration and the dose-dependent side effects associated with the repeated administration of conventional stavudine tablets.

Prasanth KR, *et al.* [11], Present investigation describes preparation of microspheres by solvent evaporation and W/O emulsion solvent evaporation methods followed by *in vitro* characterization of microspheres to evaluate the effect of method of preparation on physical properties and drug release profile of microspheres. The microspheres were found to be discrete, spherical with free flowing properties. The morphology (Scanning Electron Microscopy), particle size distribution, entrapment efficiency and their release profiles were investigated. The yield was found to be maximum in case of solvent evaporation method. The mean geometric particle size of microspheres prepared by solvent evaporation method was found in the ranges of 40-50 μm and the microspheres prepared by W/O emulsion solvent evaporation method was found in a ranges of 126-150 μm, respectively. The microspheres formulation prepared by solvent evaporation method has shown greater encapsulation efficiency than W/O emulsion solvent evaporation method. The drug carrier interactions were investigated in solid state by Fourier Transform Infrared (FT-IR) spectroscopy study._ *In vitro* drug release rate for microspheres was found to be sustained over 8 hours. Hence, it can be concluded that the formulation prepared by solvent evaporation method, has potential to

deliver Losartan potassium in a controlled manner in a regular fashion over extended period of time in comparison to all other formulations and can be adopted for a successful oral delivery of Losartan potassium for safe management of hypertension._ All data are verified as statistically significant by using one way ANOVA at 5 % level of significance ($p < 0.05$).

Sabyasachi M, *et al.* [12], in this study, fluconazole-loaded ethyl cellulose microspheres were prepared by alginate facilitated water-in-oil-in-water (w/o/w) multiple emulsion solvent evaporation technique and the effect of micro-environmental pH on the properties of microspheres was investigated. The inclusion of aqueous alginate solution of pH 6 into internal aqueous phase of the multiple emulsion led to higher drug entrapment efficiency (72.79%) of the microspheres than those prepared with solutions of either pH 4 or 8. The mean diameter of microspheres ranged from 291 to 331μm and appeared spherical under scanning electron microscope at all pH conditions. Carr's index provided an indication of free-flowing nature of all the microspheres. The drug release rate in either pH 1.2 HCl solution or pH 7.4 phosphate buffer saline (PBS) solution varied depending upon the micro-environmental pH. The release profiles of microspheres having internal pH 4 always ran higher followed by pH 8 and pH 6 in either dissolution fluids. Irrespective of micro-environmental pH, the drug release in pH 1.2 HCl solutions was slower than in pH 7.4 phosphate buffer saline (PBS) solution, when compared up to 2 h. The drug release mechanism was unaffected by the micro-environmental pH of the microspheres and was found to be controlled by Fickian diffusion. Thus, the change of pH of inner aqueous alginate phase could be beneficial for the entrapment of slightly water soluble drugs like fluconazole into ethyl cellulose microspheres.

Durga J, *et al.* [13], The objective of this investigation is to develop a multi-unit gastro retentive sustained release dosage form of a water soluble drug, Ranitidine hydrochloride, from a completely aqueous environment avoiding the use of any organic solvent, which could cure peptic ulcer more efficiently by releasing the drug especially in stomach and also for a prolonged duration of time. A new emulsion gelation technique was used to prepare emulsion gel beads using sodium alginate as the polymer. The gel beads containing oil was prepared by gently mixing or homogenizing oil and water phase containing sodium alginate which was then extruded in to calcium chloride solution. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release were studied. Minimizing the curing time of beads leaded to enhanced drug entrapment efficiency. The use of sodium

alginate and combinations of sodium alginate and pectin were used to study the effect on the sustaining property of the formed beads. It was found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug. The results show that these beads can entrap even a water soluble drug as Ranitidine hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time without using any organic solvent and any time consuming step in the preparation.

Najmuddin M, *et al.* [14], Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery system have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Ketoprofen is nonsteroidal anti-inflammatory drug with short elimination half-life. Floating microspheres of ketoprofen were prepared by solvent evaporation method using HPMC and two different grades of ethyl cellulose as polymer. The floating microsphere was evaluated such as micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microsphere. Results show that as the concentration of polymer increases it affects the particle size, percentage yield, in vitro buoyancy and drug release of microsphere. The micromeritic properties were found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation F5 prepared with HPMC 5 cps and ethyl cellulose 7-10 cps which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 98.88% for a period of 12 hrs. Results of our present study suggest that floating microsphere of ketoprofen can be successfully designed to develop sustained drug delivery which can reduce dosing frequency.

Harshad P, *et al.* [15], Mucoadhesion is topic of current interest in the design of drug delivery system. Mucoadhesive microsphere exhibit a prolonged residence time at the site of application and facilitates an intimate contact with the underlying absorption surface and thus contributes to improved or better therapeutic performance of drug. Mucoadhesive drug delivery systems promises several advantages that arise from localization at a given target site, prolonged residence time at the site of drug absorption and an intensified contact with the mucosa increasing the drug concentration gradient. Hence, uptake and consequently bioavailability of the drug is increased and frequency of dosing reduced with the result that patient compliance is improved. In recent years such Mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal for either systemic or local

effects. The principles underlying the development of Mucoadhesive microsphere and research work carried out on these systems are reviewed here.

Magharla D, *et al.* [16], to prepare and evaluate poly (ε-caprolactone) microspheres loaded with etoposide, a potent anti-cancer drug by solvent evaporation technique. **Methods:** The advent of biodegradable, polymeric drug delivery systems could be exploited successfully for maximizing the therapeutic efficacy of commonly used drugs. Etoposide was reported to be more effective when given over an extended period of time; hence poly (ε-caprolactone) microspheres of etoposide were fabricated by oil in water solvent evaporation technique by varying the polymer concentration and the amount of PVA in external aqueous phase. The prepared microspheres were characterized for entrapment efficiency, drug loading, *in vitro* release studies and subjected to particle size analysis, scanning electron microscopy; differential scanning calorimetry, Fourier transform infrared spectroscopy.

. **Pare A, *et al.* [17],** Amlodipine besylate effervescent floating tablets were developed in ten different formulations (F1 to F10) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms. F10 formulation showed maximum floating time of 24 hours and gave slow and maximum drug release of Amlodipine besylate spread over 24 hours and whereas Amlodipine besylate released from marketed tablet was rapid and maximum within 12 hours.

Kotwal A, *et al.* [18], intragastric buoyant tablets, i.e., gastro retentive drug delivery systems of Amoxicillin trihydrate were prepared with the objective to obtain site-specific drug delivery for the stomach and to extend its duration of action. The sustained release of amoxicillin is desired because of its short biological half-life. Particularly to treat *Helicobacter pylori* infections, the sustained release is desired to be confined to the stomach. The intragastric buoyant tablets of amoxicillin will provide site-specific drug delivery and thereby extend its duration of action. The dosage form was designed by using HPMC K15M and HPMC K100 polymers as gelling agents, sodium bicarbonate as gas-generating agent and other excipients. Initially granules were prepared by wet granulation technique and compressed into tablets. The pharmaceutical properties of formulations, their buoyancy lag time and total floatation time and *in vitro* drug release were evaluated. It is found that the hardness of the tablet will affect the buoyancy characteristics of the dosage form. The *in vitro* release studies indicated that the floating dosage forms containing higher concentration of HPMC K100 showed slower release. The % drug release profile was in the order of F6 > F5 > F4 > F3 > F2 > F1. The *in vitro* release data was treated with mathematical equations, and

it was concluded that Amoxicillin released from the tablet followed Peppas model with non-Fickian diffusion. Hence gastro retentive drug delivery system of Amoxycillin trihydrate is a promising approach as it can lead to decrease in the frequency of administration and ultimately lead to better patient compliance.

Sameer S, *et al.* [19], the present study was undertaken to prolong the release of orally administer. Captopril's in the floating tablets by using different grade of hydroxyl propyl methyl cellulose. Formulations were optimized using different viscosity grades of hydroxypropylmethylecellulose. Lactose and citric acid were used in different concentration as a channeling and chelating agent to obtain best optimized formulation and designed to prolong the gastric residence time (GRT). Formulations were evaluated by floating lag time and *in vitro* drug release method. Results revealed that the effect of channeling and chelating agent at different concentration had significant effect on the release of the drug from Hydrophilic matrix tablet. Three different viscosity grades of hydroxylpropylrmethyle cellulose namely K100M, K 15M and K 4M were used as a floating polymer or intention of polymer. It was observed that different viscosities not only influence the drug release from hydrophilic matrix but they also affect the floating properties of tablets. Dissolution profiles were subjected for various kinetic treatments to analyze the release pattern of the drug and we found that drug release by diffusion mechanism and followed square root kinetics or Higuchi's kinetics. The *in vitro* release profiles of drug from all the plots shows high linearity (r2= 0.9813 to 0.9954). Optimized formulations were again subjected for thickness, friability, hardness, uniformity of content, uniformity of weight, in *vitro* dissolution. Floating lag time, floating time and stability studies. Results revealed that the floating formulation of the Captopril is the best formulation to obtain better therapeutic effect and hydroxypropylrmethylecellulose at a concentration of 35% up to some extent it increases the Bioavailability of the drug to retain the dosage form on the desired site for effective period of the time.

Upendarrao G, *et al.* [20], the present investigation concerns the development of Hydro dynamically balanced tablets of Ciprofloxacin Hydrochloride, are designed to prolong the gastric residence time after oral administration and thereby increasing drug bioavailability. Floating tablets of Ciprofloxacin Hcl were prepared by direct compression using HPMC K4M and HPMC K15M as polymers along with Sodium bicarbonate as gas generating agent. The tablets were evaluated for in-vitro buoyancy, dissolution studies and physical characteristic viz. Density, Hardness, Friability, Thickness and Weight variation. Further, tablets were evaluated for in-vitro release characteristic for 12 hrs. It is found that the

hardness of the tablets affects the Buoyancy characteristic of the dosage form. All formulations possessed good floating properties with total floating time more than 12 hrs. The in-vitro release studies indicated that the floating tablets of Ciprofloxacin Hcl containing 200mg HPMC K15M (F4) showed sustained release when compared with the marketed product and provides a better option for controlled release action and improved bioavailability.

Ajay B, *et al.* [21], Ciprofloxacin HCl belong to the fluoroquinoline derivatives which is widely used in the long term therapy for treatment of a wide range of infections including anthrax, biliary tract infection, bone and joint infection, gastrointestinal including traveler's diarrhoea and *Campylobacter enteritis*, *Shiegella*, meningococcal meningitis prophylaxis, surgical infection prophylaxis, tuberculosis, leprosy and topically in the treatment of eye infections. Hence there is a potential need for floating tablet as sustained release dosage form for this drug. HPMC and carbomer are the polymers, used as suspending agent, viscosity increasing agent and tablet binder coating agents. In the present study, it was aimed to formulate floating tablet of ciprofloxacin HCl with HPMC and carbomer in different proportion (4%, 8% and 12%) by direct compression techniques using polymers lactose, Magnesium Streate, talc with sodium bicarbonate. All the prepared formulation were found to complies with the official tests like precompression parameter like angle of repose and post compression parameters like Shape, tablet dimensions, hardness, friability test, weight variation test, floating test, content uniformity and *in-vitro* dissolution study. *In-vitro* release studies were carried out using USP XXII dissolution test apparatus. The mean percentage of ciprofloxacin released at various time intervals was calculated and plotted against time. The mechanism of drug release with all the formulations was dominantly diffusion and followed zero order kinetics. It was observed that the integrity of the drug is not affected by formulation procedure. The results revealed the drug polymer ratio showed greater drug release than other formulations.

Subhash PCB, *et al.* [22], the aim of the present work was to prepare floating tablets of diltiazem HCl using xanthan gum as carrier. Diltiazem HCl is a calcium channel blocker used in treatment of several diseases of the cardiovascular system, especially angina and hypertension. It has elimination half-life of about 3.5 hrs. The formulations were prepared by varying the concentrations of xanthan gum and sodium bicarbonate. The tablets were prepared by direct compression technique using PVP K-30 as a binder and sodium bicarbonate for development of CO2. The prepared floating tablets were evaluated for tablet properties such as hardness, thickness, friability, weight variation, floating property,

compatibility using DSC and FTIR. *In vitro* dissolution was carried out for 12 hrs in 0.1N HCl at 37±0.5□C using USP basket type dissolution apparatus. It was noted that, all the prepared formulations had desired floating lag time and constantly floated on dissolution medium by maintaining the matrix integrity. The drug release from prepared tablets was found to vary with varying concentration of the polymer, xanthan gum. From the study it was concluded that floating drug delivery system can be prepared by using xanthan gum as a carrier.

Shishu *et al.* [23], 5-Fluorouracil (5-FU) has been the most widely used drug for the chemotherapy of gastro intestinal cancer for many decades.The present investigation concerns the development and evaluation of single unit fl oating tablets of 5-FU which, after oral administration, are designed to prolong the gastric residence time, increase drug bioavailability and target the stomach cancer. **Methods:** A fl oating drug delivery system (FDDS) was developed using gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxypropyl methylcellulose (HPMC) and Carbopol 934P. The prepared tablets were evaluated in terms of their physical characteristics, *in vitro* release, buoyancy, buoyancy lag-time and swelling index. The formulations were optimized for the type of fi ller, like lactose, microcrystalline cellulose (MCC) and dicalcium phosphate (DCP) as well; different viscosity grades of HPMC and concentrations.

Sreekanth S, *et al.* [24], the main aim of the study was to design and evaluate nifedipine floating matrix tablets.Hydroxy prophyl methyl cellulose (HPMC K100M) was used as a polymer. About 15-35 % of HPMC can be used as a polymer in the extended release formulations. So, here the polymer was used in the range of 16-36 %. Sodium bicarbonate (40%) is used as a gas generating agent. It can be used in the range of 25-50 %. The granules are prepared by wet granulation method. The prepared granules were evaluated for the bulk density, tapped density, bulkiness, angle of repose, compressibility index and hausner ratio. The values indicate good flow property. The compressed tablets were evaluated for hardness, uniformity of weight, friability, drug content, buoyancy lag time and duration of buoyancy. All the readings are within the prescribed limits. There was no interaction between the drug, polymer and excipients it was found out by IR studies. The *in vitro* release data were fitted to different order of reactions such as zero order, first order, higuchis reaction, Hixson crowell reaction and korsmeyer peppas reaction. The drug release follows Korsmeyers – Peppas reaction. The mechanism of drug release is by non-fickian motion. The *in vitro* drug release data indicate that the release of the drug depends upon the proportion of polymer present in the formulation. As the polymer ratio increases the release rate of the drug is prolonged.

Vaishali S, *et al.* [25], Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption in the GIT pioneered the idea of development of Gastroretentive drug delivery system. To design and evaluate the performance of GRDDS, it is important to understand the relevant anatomy and physiology of the GI tract. To achieve gastric retention, the dosage form should satisfy certain requirements; primarily, the dosage form must be able to withstand the forceful peristaltic waves in the stomach and the constant contractions, grinding and churning. To function as a gastric retention device, it must resist premature gastric emptying. Once the purpose has been served, the device should be removed from the stomach with ease. Floating DDS or hydrodynamically balanced systems (HBS) have a bulk density lower than the gastric fluids (<~1.004 g/cm^3), and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Using FDDS one can easily increase the absorption of gastric secretion-labile drug

Praveen N, *et al.* [26], Drugs with narrow absorption window in the gastrointestinal tract have poor absorption. Therefore, gastroretentive drug delivery systems (GRDDS) have been developed, which prolong the gastric emptying time. Several techniques such as floating drug delivery system, low density systems, raft systems, mucoadhesive systems, high density systems, superporous hydrogels and magnetic systems, have been employed. Floating drug delivery systems have a bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time, releasing the drug slowly at the desired rate from the system. Dosage forms available as gastric floating systems include tablets, capsules, granules and microspheres. This review on GRDDS attempts to compile the available information with all the possible mechanisms used to achieve gastric reventions.

Ferdous K, *et al.* [27], This investigation describes the preparation and *in vitro* evaluation of gastroretentive floating tablet of theophylline. Two hydrophilic cellulose derivatives, Methocel K100M and Methocel K15MCR were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount variation of theophylline on drug release profile and floating properties were investigated. Tablets were prepared by direct compression technique. Formulations were evaluated for *in vitro* buoyancy and drug release study was evaluated for eight hours using USP XXII paddle-type dissolution apparatus using 0.1N HCl as dissolution medium. The release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The release rate, extent and mechanisms were found to be

governed by polymer and floating agent content. The content of active ingredient was also a vital factor in controlling drug release pattern. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 hours, release rate constant and diffusion exponent.

Anil G, *et al.* [28], the present study was undertaken with an aim to formulation development and evaluation of gastroretentive floating tablets of venlafaxine hydrochloride, which releases the drug in a sustained manner over a period of 12 hours. Three different viscosity grades of Hydroxypropyl methylcellulose (HPMC) namely K4M, K15M, and K100M were used for the preparation of tablets. The tablets were prepared by direct compression and evaluated for tablet thickness, weight variation, tablet hardness, friability, in vitro buoyancy test, in vitro drug release and Fourier transform infrared (FT-IR) spectroscopy. Formulation F3 can be considered as an ideal or optimized formulation for gastroretentive floating tablet of venlafaxine HCl. The optimized formulation showed sufficiently sustained drug release and remained buoyant on the surface of the medium for more than 12 hours. As the concentration of HPMC increases in the formulation the drug release rate was found to be decreased. It can be concluded that floating drug delivery system of venlafaxine HCl can be successfully formulated as an approach to increase gastric residence time and thereby improving its bioavailability.

Vishnu MP *et al.* [29], Verapamil hydrochloride using different hydrocolloid polymers including Carbopol (CP 934P; CP 940P), Hydroxypropylmethylcellulose (HPMC K4M; HPMC K15 M; HPMC E15) and Xanthan gum was done by the direct compression technology. The tablets were evaluated for the physicochemical parameters such as weight variation, thickness, friability, hardness, drug content, in vitro buoyancy studies, swelling index study, in vitro dissolution studies. The prepared tablets exhibited satisfactory Physico-chemical characteristics. Tablet bouncy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The in vitro dissolution studies were carried out in a USP XXII apparatus 2 in 0.1N HCl. All the gastro retentive tablets showed good in-vitro buoyancy. The tablet swelled radially and axially during in-vitro buoyancy studies. The selected tablets (F6) containing Xanthan gum released approximately 97.89% drug in 24 h in vitro dissolution study, while the buoyancy lag time was 24.6 ± 3.2 second and the tablet remained buoyant for > 24 h. Zero order and non-Fickian release transport was confirmed as the drug release mechanism for the selected tablets (F6). Tablets (F6) showed no significant change in physical appearance, drug content, total buoyancy time or in vitro dissolution study after storage at 45 °C/75% RH for three months.

3. DRUG PROFILE[30]

Name: Felodipine

Description:

Felodipine is a long-acting 1,4-dihydropyridine calcium channel blocker (CCB)b. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, Felodipine prevents calcium-dependent myocyte contraction and vasoconstriction. Felodipine is the most potent CCB in use and is unique in that it exhibits fluorescent activity. In addition to binding to L-type calcium channels, Felodipine binds to a number of calcium-binding proteins, exhibits competitive antagonism of the mineralcorticoid receptor, inhibits the activity of calmodulin-dependent cyclic nucleotide phosphodiesterase, and blocks calcium influx through voltage-gated T-type calcium channels. Felodipine is used to treat mild to moderate essential hyperten.

Structure:

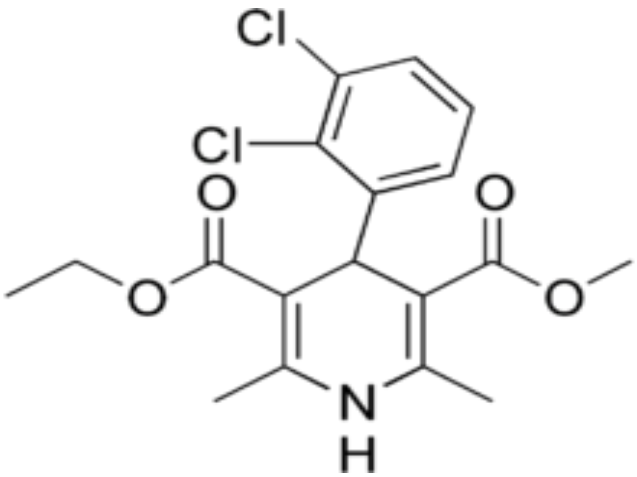


Fig. 11: Structure of felodipine

IUPAC name: 3-ethyl 5-methyl 4-(2, 3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Molecular formula: $C_{18}H_{19}Cl_2NO_4$

Molecular weight: 384.259 g/mol.

Half-life: 2 hrs- 4.8 hrs

Mechanism of action:

Felodipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through voltage-gated L-type calcium channels. It reversibly competes against nitrendipine and other DHP CCBs for DHP binding sites in vascular smooth muscle and cultured rabbit atrial cells. Calcium ions entering the cell through these channels bind to calmodulin. Calcium-bound calmodulin then binds to and activates myosin light chain kinase (MLCK). Activated MLCK catalyzes the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Signal amplification is achieved by calcium-induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. Inhibition of the initial influx of calcium decreases the contractile activity of arterial smooth muscle cells and results in vasodilation. The vasodilatory effects of Felodipine result in an overall decrease in blood pressure. Felodipine may be used to treat mild to moderate essential hypertension.

Protein binding: 99%, primarily to the albumin fraction.

Metabolism: Hepatic metabolism primarily undergoes via cytochrome P450 3A4. Six metabolites with no appreciable vasodilatory effects have been identified.

Route of administration: oral

Dose: 200 mg per/day.

4. POLYMERS PROFILE[31]

4.1 SODIUM ALGINATE

Nonproprietary Name:

BP: Sodium Alginate

PhEur: Sodium Alginate

USP-NF: Sodium Alginate

Synonyms: algin, alginic acid, sodium salt, sodium polymannuronate

Chemical Name: Sodium alginate

Empirical Formula:

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic

Structure:

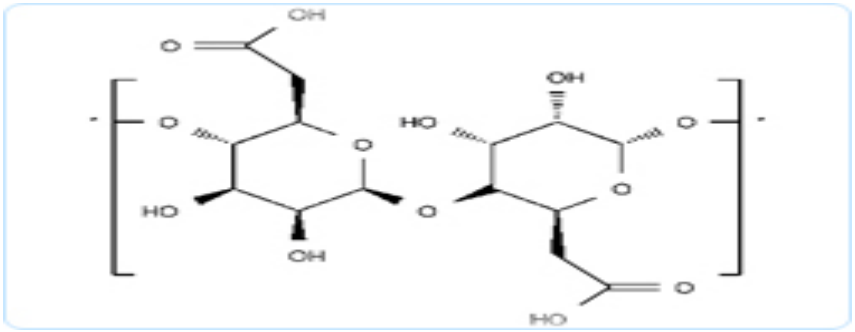


Fig. 12: Structure of Sodium alginate

Molecular formula: ($C_6H_7O_6Na$)

Description:

White or light yellow, vagiform powder, odorless, tasteless, dissolve in water, insoluble in ethanol and ether.

Method of Manufacture:

Alginic acid is extracted from brown seaweed and is neutralized with sodium bicarbonate to form sodium alginate.

Acidity/alkalinity: pH _7.2 for a 1% w/v aqueous solution.

Functional Category:

Stabilizing agent, suspending agent, tablet and capsule disintegrant, tablet binder, viscosity increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant; it has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions.

Description:

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

Solubility:

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Slowly soluble in water, forming a viscous colloidal solution.

Viscosity (dynamic):

Various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity. Typically, a 1% w/v aqueous solution, at 20^0C, will have a viscosity of 20–400 mPa s (20–400 cP).

Stability and Storage Conditions:

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidity and a cool temperature.

Incompatibilities:

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenyl mercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%.

Method of Manufacture:

Alginic acid is extracted from brown seaweed and is neutralized with sodium bicarbonate to form sodium alginate.

Safety:

It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

Applications:

- Sodium alginate is used in a variety of oral and topical pharmaceutical formulations.
- In tablet formulations, sodium alginate may be used as both a binder and disintegrates
- It has been used as a diluent in capsule formulations
- Sodium alginate has also been used in the preparation of sustained release oral formulations since it can delay the dissolution of a drug from tablets, (5–7) capsules,(8) and aqueous suspensions.
- In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions.
- Sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic-solvent systems.
- It has also been used in the formation of nanoparticles.

4.2 HYDROXY PROPYL METHYLCELLULOSE

1. Nonproprietary Name:

BP: Hypromellose,USP: Hypromellose

2. Synonyms:

Hydroxypropyl methylcellulose, HPMC, hypromellosum, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, MHPC.

3. Chemical Name: Cellulose hydroxypropyl methyl ether

4. Empirical Formula and Molecular Weight:

The PhEur 6.3 describes hypromellose as a partlyO-methylated and O-(2-hydroxypropylated) cellulose. Molecular weight is approximately 10 000–1 500 000.

5. Structural Formula:

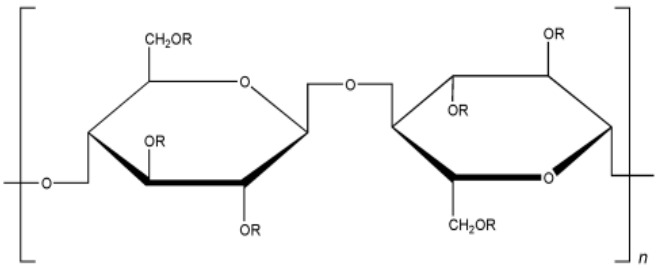


Fig. 13: Structure of HPMC

Where R is H, CH_3, or $CH_3CH(OH)CH_2$

6. Applications in Pharmaceutical Formulation or Technology:

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.

7. Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

8. Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane.

9. Stability and Storage Conditions:

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

10. Safety:

Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have a laxative effect.

4.3 PEG 4000

PEG 4000 Is a Mixture of the poly condensation products of ethylene oxide and water obtained under controlled conditions.

Molecular formula: $HOCH_2(CH_2OCH_2)_nCH_2OH$.

Description:

A creamy white, wax like solid, powder (or) flakes, odour faint and characteristic.

Functional use: It is used as a clarifying agent, Carrier.

Solubility*:* Soluble in water.

5. AIM AND OBJECTIVE

Floating drug delivery of particular interest for drugs that act locally in the stomach, and are primarily absorbed in the stomach, they are poorly soluble at an alkaline pH, and have a narrow window of absorption, and which are unstable in the intestinal or colonic environment. To provide good floating behavior in the stomach the density of the device should be less than that of the gastric contents.

Drugs that have narrow absorption window in upper part of released GI tract i.e., stomach and small intestine, which is due to short transit time of dosage form formulation of this drug leave upper part of tract and reaches to non – absorbing distal regiment, resulting lesser bioavailability. Floating drug delivery systems prolong the drug release rate from formulation in the stomach and upper part of small intestine until all drugs are released for the desired period of time.

The drug of choice felodipine is an effective anti-hypertensive drug. The main purpose of the present research was to develop a controlled drug delivery system of felodipine for pre-oral administration using biocompatible sodium alginate polymer in order to increase its biological half life and determine the influence of formulation and preparation variables on micro particles characteristics such as, drug incorporation and *in-vitro* drug release.

6. PLAN OF WORK

The present work carried out to prepare and evaluate the floating microsphere the following experimental protocol was therefore design to allow a systemic approach to study

- Preformulation studies
    - FT-IR study
    - Preparation of standard curves
- Formulation of floating microspheres
- Evaluation tests
    - Tapped density
    - Angle of repose
    - Compressibility index
    - Drug entrapment
    - Particle size analysis
    - Percentage yield
    - Floating behavior of microspheres
    - Scanning electron microscopy
    - In vitro release study
    - Stability study

7. MATERIALS AND EQUIPMENT

Table no.4: MATERIALS USED

S. No	Chemical Name	Supplier
1	Felodipine	Micro labs, Pvt, Ltd Bengaluru
2	PEG 4000	Lobachemi, Pvt Ltd.Mumbai
3	Sodium alginate	Lobachemi, Pvt Ltd.Mumbai
4	HPMC K 100	Lobachemi, Pvt Ltd.Mumbai
5	Ethonol	S.D fine chemicals Pvt Ltd, Mumbai
6	Dichloro methane	Merck Pvt Ltd, Mumbai
7	Conc.HCL	Nice chemicals, Pvt Ltd, Cochin
8	Tween 80	S.D fine chemicals Pvt Ltd, Mumbai
9	n-hexne	Qualigens fine chemicals pvt ltd. India

Table no. 5: EQUIPMENTS USED

S. No	Name of the Equipment	Supplier
1	Pippetes,Beakers	Borosil
2	Hot air oven	Sunbimmanfacture Pvt. Ltd
3	Uv-spectro photo meter	Shimadzu
4	Dissolution apparatus	Electro lab
5	Magnetic stirrer	Sunsim, India
6	PH meter	Elico
7	Scanning eletron microscopy	JEOL, JSM-670F,Japan
8	sieve	Jayanth scientific IND, Mumbai
9	FT –IR apparatus	Shimadzu

Preformulation studies

8.1 FT-IR STUDIES[10]:

The FT-IR analysis was done conducted for the analysis of drug polymer interaction andstability of the drug during microencapsulation process. The FT-IR spectrum of pure felodipine, sodium alginate, HPMC K 100, and PEG 4000.was studied. The physical mixtures of the floating microspheres formulation also were recorded.

8.2 UV-Visible Spectroscopy:

Standard graph of Felodipine:

The Stock solution of felodipine was prepared by accurately dissolving 100 mg in 100 ml of acidic buffer of pH 1.2. From this 10ml was taken and diluted up to 100 ml with acidic buffer pH 1.2 to get 100 µg/ml solutions. From this 10µg/ml solution was prepared by diluting 10ml to 100ml with acidic buffer pH 1.2. From this 2, 4, 6 & 8 to 10 ml with acidic buffer pH 1.2.

8.3 Preparation of Floating Microspheres:

Table no. 6: Formulation of floating microsphere

Formulation	Drug	PEG 4000	Sodium alginate	HPMC K 100
F1	100 mg	300 mg	-	-
F2	100 mg	500 mg	-	-
F3	100 mg	-	300 mg	-
F4	100 mg	-	500 mg	-
F5	100 mg	-	-	300 mg
F6	100 mg	-	-	500 mg

The formulation of the floating microsphere was performed by taking the drug and the polymer in the ratio of 1:3 and 1:5. The floating microspheres were prepared by solvent evaporation method

SOLVENT EVAPORATION METHOD: [30]

The solvent evaporation method for felodipine microsphere was as follows:

1 a) Preparation of sodium alginate solution, HPMC K100, PEG 400 the ratio of 1:3

Weighed amount of sodium alginate was added into 100 ml of distilled water in 250ml beaker. The remaining HPMC K100 and PEG 4000 also prepared individually.

b) Preparation of sodium alginate solution, HPMC K100, PEG 400 the ratio of 1:5

Weighed amount of sodium alginate was added into 100 ml distilled water in 250 ml beaker. and similarly The remaining HPMC K100 and PEG 4000 were also prepared individually.

2) Preparation of organic phase:

0.5 ml ground nut oil was added into the 100 mg of felodipine in 100 ml beaker.

3) Preparation of $cacl_2$ solution:

40 gms of $cacl_2$ was added in 200 ml distilled water in 250 ml beaker. The sodium alginate, HPMC K100, PEG 4000, solutions were added into oily phase (organic phase) individually. So ultimately primary solutions were prepared. With the help of micro syringe above prepared primary emulsions were added in the 20% $CaCl_2$ solution. Before the addition of primary into 20% $cacl_2$ which was kept initially on magnetic stirrer with a constant speed set at 200 rpm and at constant room temperature (37.5±1 ºcelcius), n-hexane was added to avoid the collapse of drops of primary emulsions during the addition in 20% $CaCl_2$,because n-hexane play an important role in microsphere formation.

8.4 Evaluation tests:

The following parameters are determined for floating microspheres of felodipine.

8.4.1. Tapped Density: [32, 33]

The floating microspheres were tapped gently as surface till the powder occupies maximum volume and noted the volume as tapped volume. The mechanical tapping of cylinder was carried out manually 500 times. The tapped density was calculated in g/cm^2 by the following formula.

$$\text{Tapped density} = \frac{\text{weight of microspheres}}{\text{Tapped volume}}$$

8.4.2. Angle of Repose: [32, 33]

S.N0	Angle of repose (θ)	Carr's index	Type of flow
1	<25	5-15	Excellent
2	25-30	12-16	Good
3	30-40	18-21	Passable
4	-	23-35	Poor
5	-	33-38	Very poor
6	>40	>40	Extremely poor

The frictional forces in floating microspheres can be measured by the angle of repose θ. This is the maximum angle possible between the surface of a pile of microspheres and the horizontal plane.

A funnel is fixed at a particular height 'h' on a burette stand. A white paper is placed bellow the funnel. The sample is passed slowly through the funnel until it forms a pile further addition of drug stopped as soon as the drug pile touches the tube of the funnel. Circle of the pile of drug is drawn without disturbing the pile of radius of the pile is noted. Angle of repose is calculated from the following formula: **Table no. 7:**

$$\mathbf{Tan\theta = h/r}$$

Θ=angle of repose degrees, h=height of pile, r=radius of the pile in cm

8.4.3. Carr's compressibility index: [32, 33]

The percentage compressibility index was calculated according to following formula.

$$\mathbf{\%compressibility\ index = [1-V/V_0] \times 100}$$

Where V and V_O are the volume of the sample after and before the standard tapping respectively. Each determination was made in triplicate.

8.4.4 Drug entrapment: [34]

The various formulations of the floating microspheres were subjected for drug content. 100mg of floating microspheres from all batches were accurately weighed. The microspheres were dissolved with 10ml ethanol in in 100ml volumetric flask and makeup the volume with 1.2 pH acidic buffer. The resulting solution is then filtered through whatmann

filter paper no 44.after filtration, from the solution 10ml was taken out and diluted up to 100ml with pH1.2 .again from the solution taken out and diluted up to 10ml with pH1.2 and the absorbance was measured at 362nm against pH1.2 as blank. The percentage drug entrapment was calculated as follows.

$$\%\text{drug entrapment} = \frac{\text{calcuted drug concentration}}{\text{theoretical drug concentration}} \times 100$$

8.4.5 Particle size analysis: [32, 33]

Particle size analysis plays an important role in determining the release characteristic and floating property. The size of floating microspheres were measured by using an optical microscope, and the mean practical size was calculated by measuring nearly 200 particles with the help of calculated ocular micrometer.

8.4.6 Percentage yield: [14]

The prepared microspheres weighed from different formulations the measured weight was divided by the total amount of all non -volatile components which were used for the preparation of microspheres.

$$\textbf{percentage yeild} = \frac{\textbf{actual weight of product}}{\textbf{total weight of drug and polymer}} \textbf{ x 100}$$

8.4.7 Buoyancy percentage: [30]

100 mg of floating microspheres were placed in pH1.2 (900ml) containing 0.02% of tween80.the mixture was stirred with paddle at 100 rpm. The layer of buoyant microsphere was pippeted and separated by filtration at 1, 2,3, 4, 5,6,7,8,10, and 12.hrs the collected microspheres were dried in a desiccators over night. The percentage of microspheres was calculated by the following equation:

$$\textbf{percentage floating microspheres} = \frac{\textbf{weight of floating microsphere}}{\textbf{intial weight of floating microsphere}} \textbf{ x 100}$$

.

8.4.8 Scanning electron microscopy: [36]

Dry microspheres were placed on an electron microscope brass stub encoated with gold in an ion sputter.Then picture of microsphere were taken by random scanning of stub. The SEM analysis of the microspheres was carried out by using JEOL, JSM-670F japan (Sastra University, tanjavur).the microspheres were viewed at an accelerating voltage of 3.0.

8.4.9 *In-vitro* Drug release studies: [35]

The drug release rate from floating microspheres was carried out using the USP type – II dissolution basket assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were discrete in 900 ml of pH1.2 maintained at 37±0.5 ºC and stirred at 100 rpm. 1ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were suitably diluted with pH 1.2 and analyzed spectrophtometrically at 362 nm to determine the concentration of drug present in the dissolution medium.

8.4.10 Stability studies: [22]

The stability study was carried out for the all formulations by exposing it to different temperatures 5-8 ºC, 27 ºC and 40 ºc for 3 months. The samples were analyzed for drug content at the regular intervals.

9. RESULTS AND DISCUSSION

9.1 FT-IR Studies:

The drug and polymer interaction was studied by taking FT-IR .Infrared spectra of drug and polymers were carried out by using KBR pellet technique. The spectrum was observed for the drug and the polymers individually and when the drug mixed with the different polymers and the range of the mixture was compared with the drug to find whether there is any drug polymer interaction.

S. No	Type of bond	Standard wave number	Observed wave number			
			Felodipine	Felodipine + Sod. Alginate	Felodipine + PEG4000	Felodipine +HPMC
1	N-H	3400	3370.72	3368.79	3371.68	3457.52
2	C-X chloride	785-540	729.12	729.12	731.05	728.15
3	C =C aromatic	1600 & 1475	1620.26 1495.85	1616.40 1497.78	1620.28 1494.88	1611.58 1460.16
4	C=O	1725-1700	1697.41	1706.09	1620.26	1708.99
5	O-H	3500	3506.70	3629.19	3636.90	3457.52
6	C-O	1300-1000	1307.78	1307.78	1308.75	1008.85
7	C-H (stretch)	3000-2850	2983.98	2901.04	2881.78	2990.76
8	$-CH_3$ (Bend)	1450& 1375	1436.05 1381.08	1430.26 1364.68	1472.70 1350.22	1460.16 1371.43
9	$-CH_2$ (Bend)	1465	1495.85	1497.78	1472.70	1460.16
10	Alkenes (stretch)	3100-3000	3097.78	3093.92	3232.80	3071.74

Table no 8: Functional group Analysis of drug and Polymers

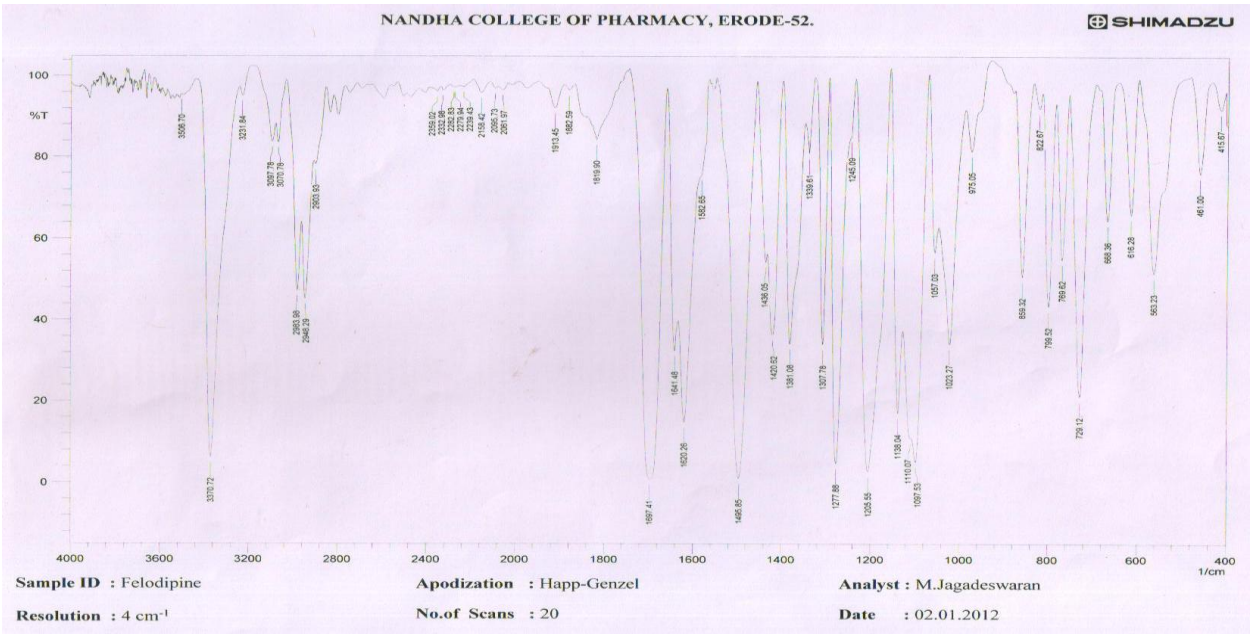


Fig: 15 Spectra of Felodipine

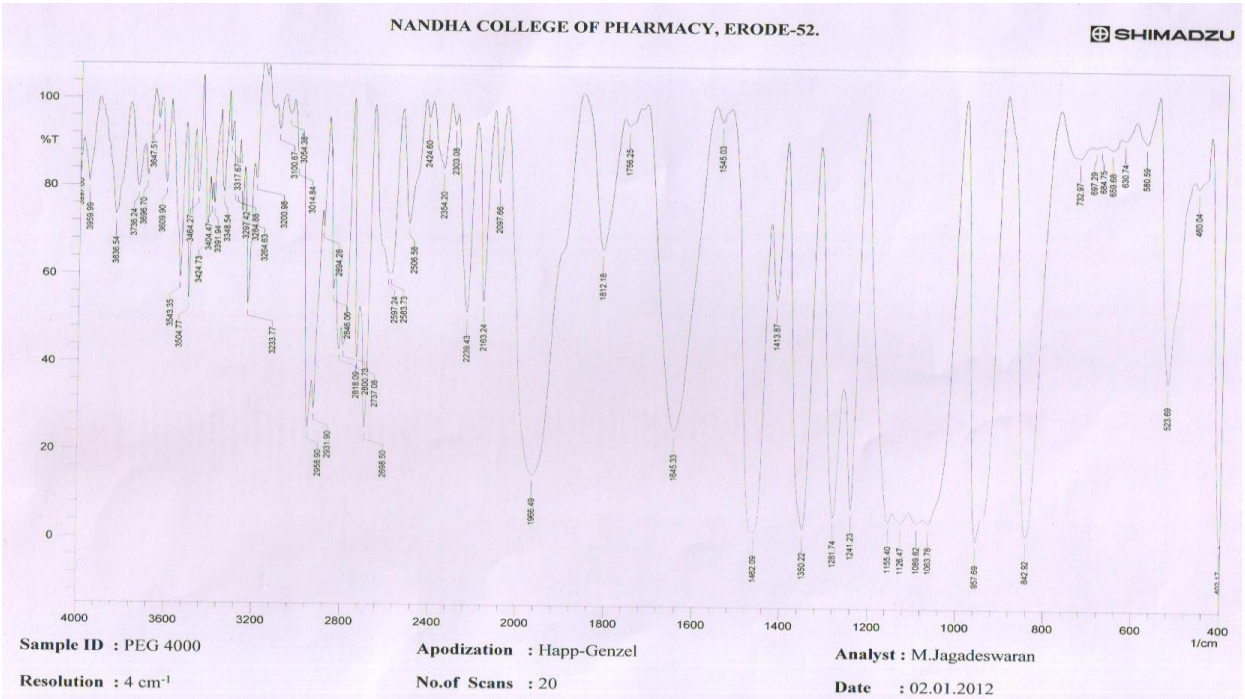


Fig: 16 Spectra of PEG 4000

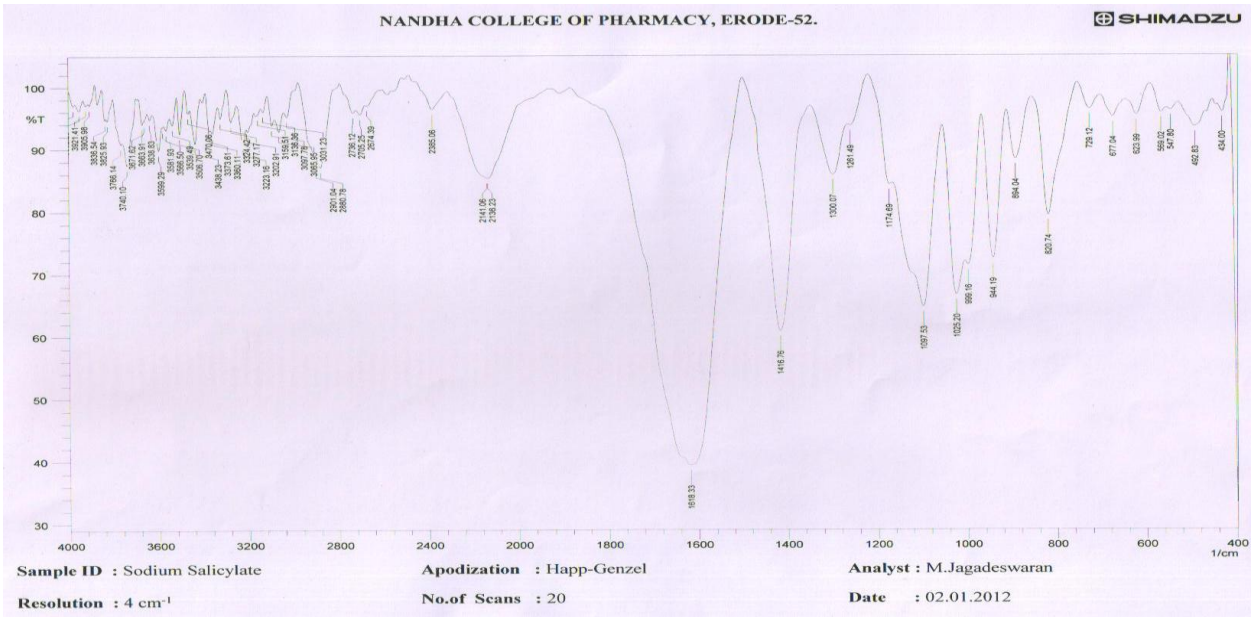


Fig: 17 Spectra of sodium alginate

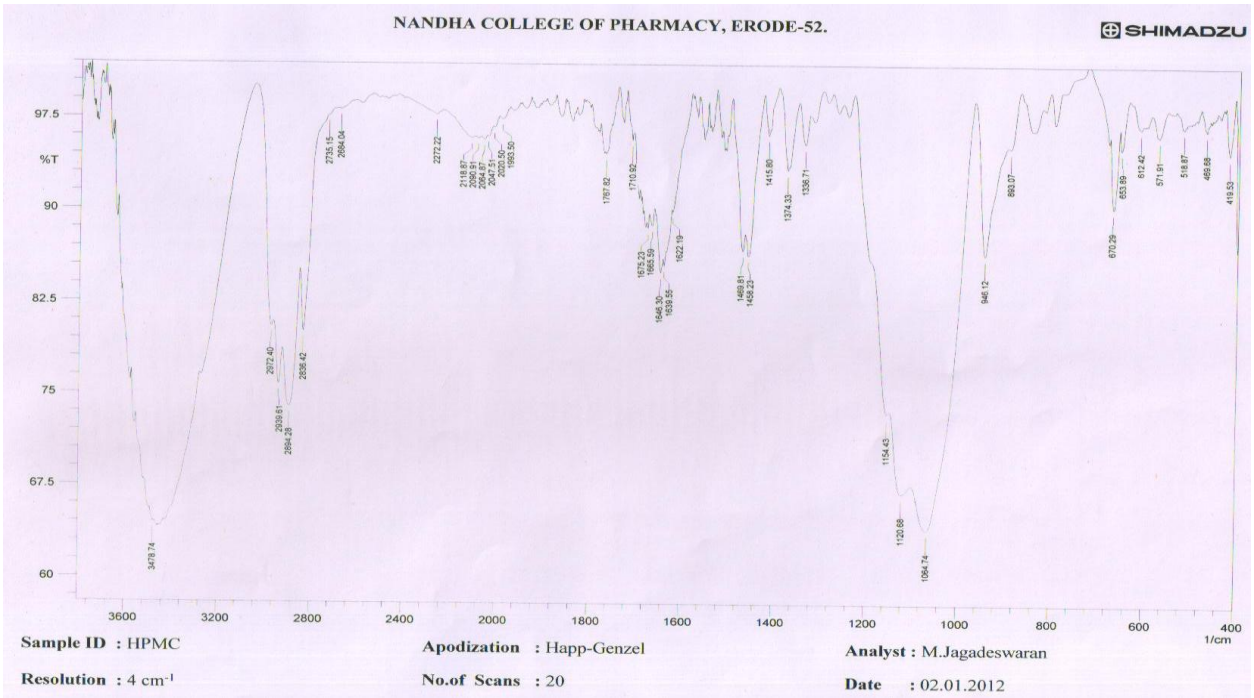


Fig: 18 Spectra of HPMC

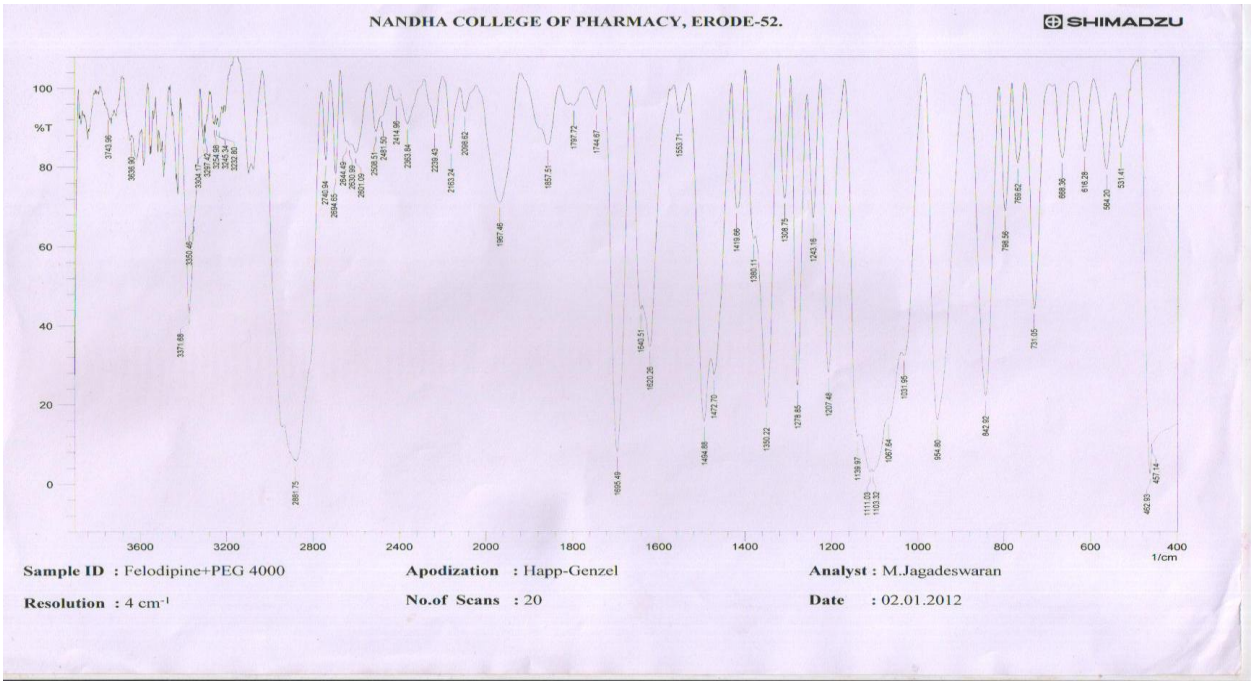


Fig: 19 Spectra of Felodipine with PEG4000

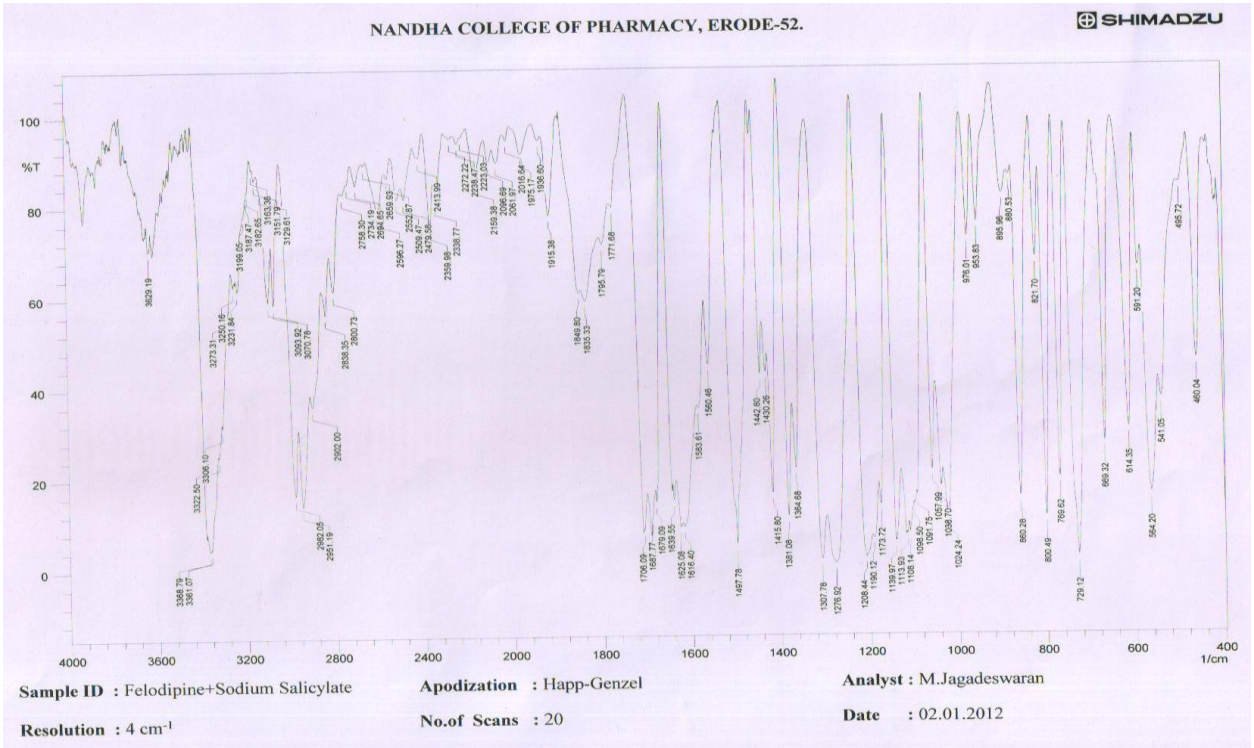


Fig: 20 Spectra of Felodipine with sodium alginate

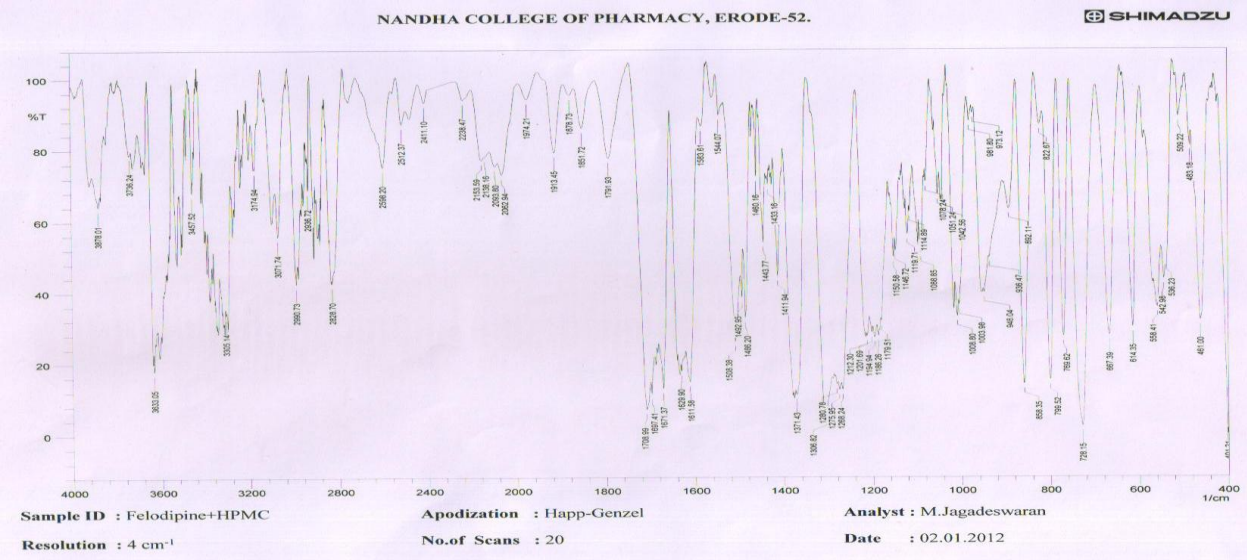


Fig: 21 Spectra of Felodipine with HPMC

The results showed that there was no drug polymer interaction when IR spectra of pure drug felodipine in the presence of PEG 4000, sodium alginate and HPMC K 100, thus revealing compatibility of the selected drug in different polymers.

9.2 Standard Graph of Felodipine:

Different concentrations of felodipine from 2 to 10µg/ml were prepared and the absorbance was taken at 362 nm against pH1.2 acidic buffer and graph was plotted between concentration and absorbance.

Table no. 9: Spectrophotometric analysis of formulation

S.No	Concentration(µg/ml)	Absorbance
1.	0	0
2.	2	0.205
3.	4	0.422
4.	6	0.580
5.	8	0.842
6.	10	0.934

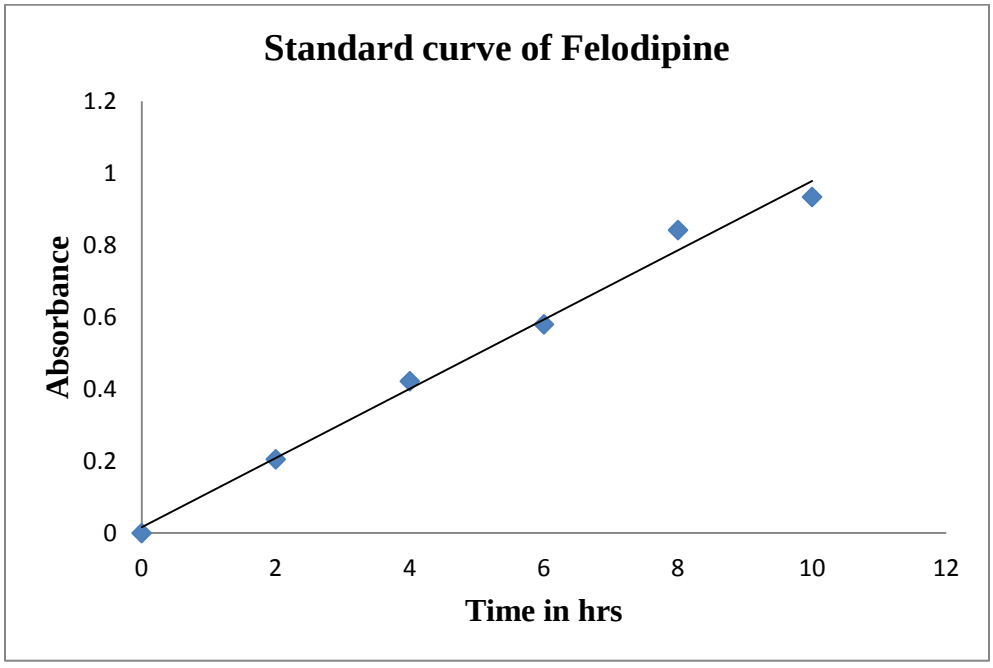


Fig: 22

9.3 Evaluation of microspheres:

9.3.1 Tapped density:

The tapped density was determined by tapping method the tapped density value of different microspheres range from 0.303 – 0.402 g/cc as shown in the table.

Table 10

Formulation	Tapped density g/cc
F1	0.321
F2	0.303
F3	0.402
F4	0.383
F5	0.364
F6	0.326

9.3.2 Angle of repose:

Angle of repose of microspheres was determined by fixed funnel method. Angle repose of microspheres was in range of 24º36’ - 33º58’as shown in Table. All formulation showed excellent flow ability as represented in term of angle of repose.

Table 11

Formulation	Angle of repose
F1	29º31’
F2	27º59’
F3	28º47’
F4	26º51’
F5	30º38’
F6	29º54’

9.3.3 Compressibility index:

It is determined by same tapping method and its range was found to be 9.37-19.81% the results was as shown in the table. The compressibility index less than 20% was suggested for all formulations excellent flow property. The flow properties of the microspheres have been expressed in terms of carr's index. The carr's index for all formulation was good and in the passable range, which indicates good flow property and suggested that the microspheres could be easily handled during the processing.

Table 12

Formulation	Compressibility index %
F1	17.59
F2	19.81
F3	9.37
F4	12.46
F5	14.23
F6	16.78

9.3.4 Drug entrapment:

Table 13

Formulation code	Drug entrapment
F1	55.6
F2	58.6
F3	61.2
F4	64.6
F5	59.2
F6	56.7

The drug entrapment efficacies of different formulations were in range of 55.8 - 64.4%w/w.as shown in the table. Drug entrapment efficacy slightly decreased with increase HPMC K100 content ratio in microspheres. This is due to the permeation characteristic of HPMC K100 that could facilitate diffusion of part of entrapped drug to surrounding medium during preparation of floating microspheres. It was observed that the microspheres of all the

formulations that the core coat ratio of 1:5 gave highest encapsulation of the drug when compared to the ratio of 1:3. The drug loading of felodipine microspheres decreased with increase in the concentration of polymer and drug entrapment efficiency of felodipine floating microspheres increase with the increase in the concentration of the polymer.

9.3.5 Particle size analysis:

Table 14

S.No	Formulation code	Mean particle size (µm)
1	F1	723
2	F2	796
3	F3	862
4	F4	897
5	F5	675
6	F6	689

The particle size was determined by optical microscopy method.It plays an important role in floating ability and drug release. If size of microspheres is less than 500µg release rate of drug will be high and floating ability will reduce, microspheres ranges between 500µm - 1000µm,the floating ability will be more and release rate will be in sustain manner.

The mean particle size of microspheres was in range 675-897µm.the results were tabulated in the table 14.The particle size distribution was almost uniform and narrow in all the formulations. It was observed that microspheres with core coat ratio of 1:3 were of less in size, when compared to the particle size of 1:5. This may be due to the viscosity of the polymers used.

9.3.6 Percentage yield:

Table 15

Formulation code	Percentage yield
F1	64.2
F2	61.8
F3	78.3
F4	72.8
F5	59.2
F6	53.7

The percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of developed formulations of felodipine floating microspheres F1-F6 were found to be in the range of 53.7 -78.3%.

9.3.7 Floating behavior of microspheres:

Table 16

Time (Hrs.)	Formulations floating behavior					
	F1	F2	F3	F4	F5	F6
1	84.61	81.35	96.39	93.13	89.23	87.16
2	78.05	75.74	94.11	91.09	86.73	83.19
4	71.82	68.94	91.76	88.71	79.84	75.02
6	66.79	61.96	84.19	80.91	74.20	71.33
8	62.93	57.71	81.34	78.47	68.51	61.68
10	53.68	51.87	79.73	76.68	63.17	58.75
12	51.76	45.08	73.62	70.23	59.06	55.92

Microspheres was dispersed in PH 1.2 containing Tween 80 (0.02% w/w) to simulate gastric fluid. The F3-F4 Formulations shows best floating ability (96.39-70.23%) in 12 hours. Comparatively the remaining formulations showed less floating ability the floating ability of all formulations within the range of (45.08 -96.39 %). as showed in Table- 16. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent

gelation. It was found that the felodipine microspheres of the formulation F3 showed desirable buoyancy and adequate release characteristics.fig 23

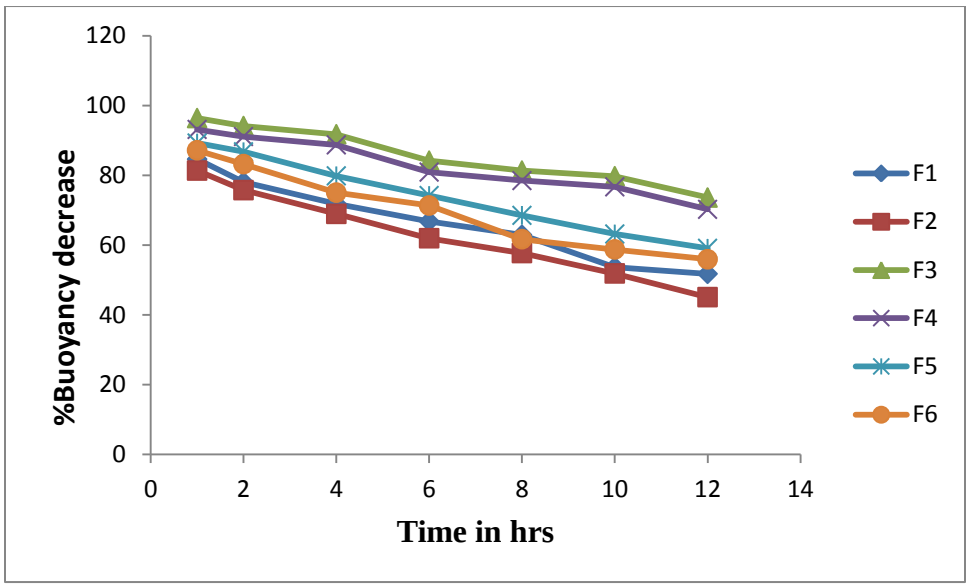


Fig 23

9.3.8 Scanning Electronic Microscopy:

Shape and surface characteristics of microspheres were examined by Scanning Electron Microscopy. Surface morphology of F3 formulation was examined at an different magnification of 40X and 200X, which illustrate the smooth surface of floating microspheres and small hollow cavity present in microspheres which is responsible for floating property. SEM revealed pores on the microsphere as well as hollow microsphere interior. The surface morphology internal structure of microspheres was determined by SEM as shown in figure 24. From this figure it was observed that so many pores are formed due to the drug release. Some pores may be small on big in size due ot the blasting of the drug.

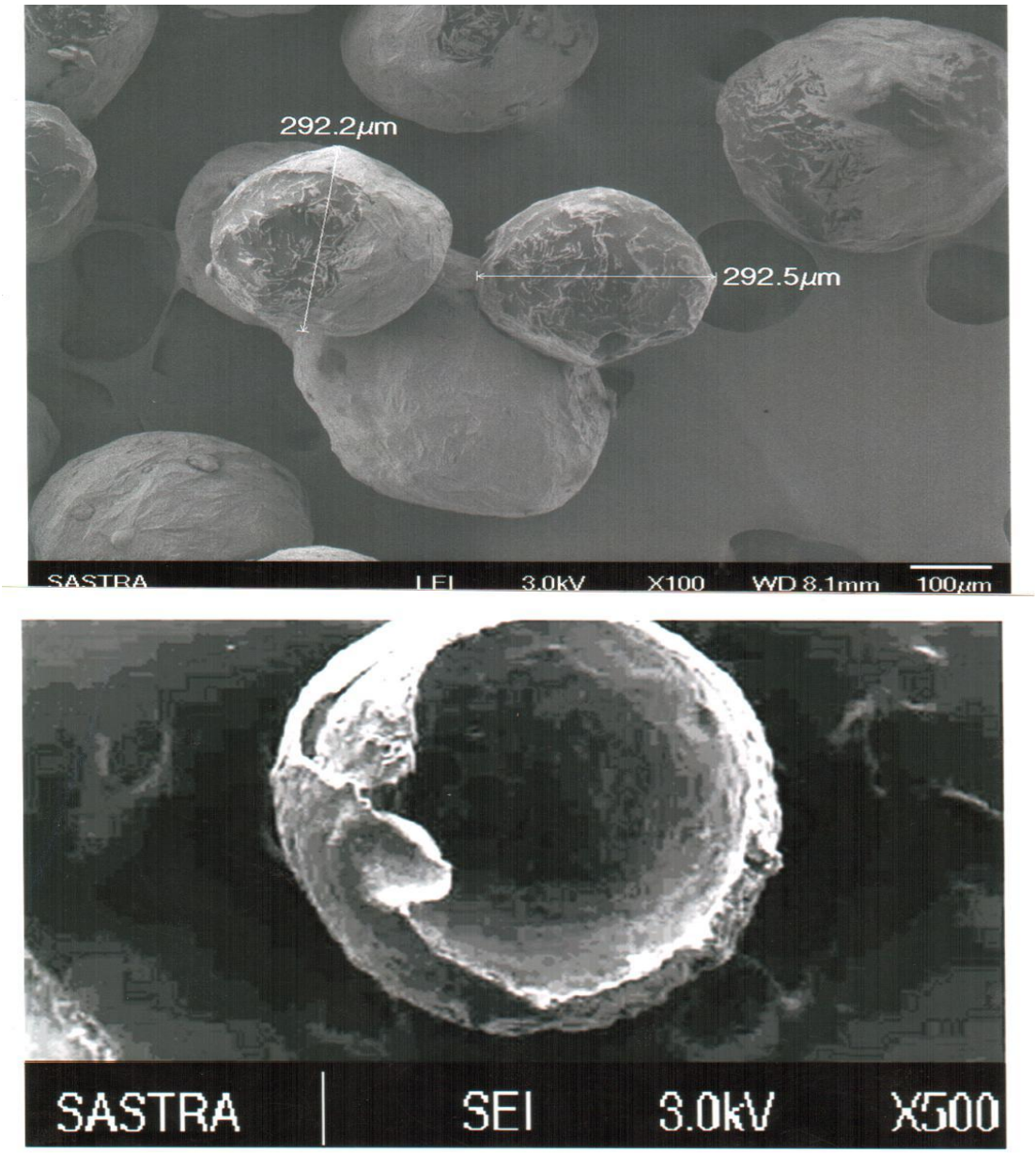

292.2µm
292.5µm
SASTRA LEI 3.0kV X100 WD 8.1mm 100µm
SASTRA SEI 3.0kV X500

Fig 24

9.3.9 Dissolution studies:

Table 17

Time (Hrs.)	Percentage drug released					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	3.62	3.50	9.82	8.42	9.64	7.23
2	15.43	12.42	27.28	19.46	23.40	11.39
3	25.72	24.75	38.03	36.45	30.72	34.22
4	33.06	31.72	56.07	42.39	36.51	39.76
5	38.98	37.87	63.41	48.47	44.12	46.31
6	45.02	43.93	71.51	56.39	49.14	50.13
7	52.10	50.62	77.60	63.25	57.78	55.76
8	60.51	56.86	82.51	70.26	65.43	61.42
10	69.92	61.92	88.53	80.25	76.98	67.31
12	76.10	68.98	93.72	86.04	81.93	73.97

The drug release data obtained for the formulations from F1 –F6 were tabulated in the table 17. The *in-vitro* release studies of the floating microspheres were studied for all the formulations. The cumulative percentage drug released from floating microspheres decreased with increase in concentration of polymers PEG 4000, Sodium alginate and HPMC K 100 respectively.

Among the definite felodipine floating microspheres formulations, the formulation F3 was selected as the ideal formulation based on its micrometrics properties, spherical in shape, floating behavior, drug loading, drug entrapment efficiency and percentage of drug release over a prolonged period over 12hrs (fig 25) for further studies like stability study.

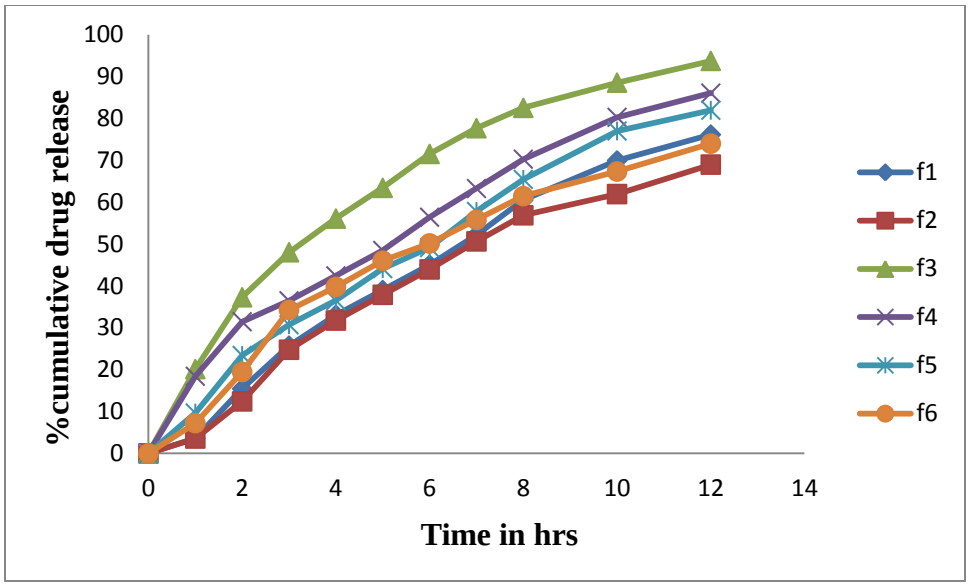


Fig 25

9.3.10 Stability studies:

Table 18

S. No	Days	% Drug retained 5-8ºC	% Drug r retained 27ºC	% Drug retained 42ºC
1	0	100±00	100±00	100±00
2	30	94.6±0.015	94.9±0.003	94.7±0.041
3	45	94.4±0.013	94.7±0.027	94.3±0.036
4	90	94.2±0.15	94.3±0.012	94.1±0.02

The stability study was carried out for the F3 formulation by exposing it to different temperatures 5 -8ºC, 27ºC and 40ºC for 3 months. The sample was analyzed for drug content regular intervals.it was found that no remarkable change in the drug content in F3 formulation. This indicates that F3 was stable for following temperature. The drug release profile indicated that there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence it can be concluded from the results that the developed felodipine floating microspheres were stable and retained their pharmaceutical property over a period of 3 months.

10. CONCLUSION

Drug absorption in the GIT is a highly variable process, prolonging gastric retention of the dosage forms and extends the time of the drug absorption. Floating microspheres are prepared with enteric coated polymer (sodium alginate) [successfully by the solvent evaporation technique]. Upon incorporation of the hydrophilic polymer, such as HPMC I the shell of microspheres, the amount of drug released from microspheres could be enhanced. In-vitro data obtained from floating microspheres of felodipine showed excellent flow ability, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Thus, the prepared floating microspheres may prove to the potential candidates for multiple unit delivery devices adaptable to any intra-gastric conditions.
The formulation were evaluated for various micrometrics and characteristic studies. It increases the bioavailability of dosage form with prolonged effect, hence improves the patient compliance.
Mean particle size for all formulations were varied, due to change in drug polymer ratio. True density and tapped density values for all formulations were less than of that gastric fluid (1.004 gm/cm^3) exhibits good buoyancy. Angle of repose ($<40^0$) for all formulations showed excellent flow ability.

Drug release pattern was evaluated in 0.1 N HCl (pH 1.2). Release rate of F1, F2, F6 formulations were found to be slow and incomplete in dissolution medium. Ideal property of floating microspheres includes high buoyancy and sufficient release of drug in pH 1.2. it necessary to selected appropriate balance between buoyancy and drug release rate from all developing floating microspheres.

F3 formulation showed best appropriate balance between buoyancy and drug release rate, which can be considered as a best fit for floating microspheres. The design system F3 floats in the stomach and prolongs the gastric residence time (GRT). Consequently, it provides sustained action. In addition, floating microspheres enabled increase drug absorption rate, as it gradually sink in the stomach and arrived at the absorption site. The developed formulation overcomes the drawbacks and limitations of sustained release preparations. Therefore multiple unit floating systems, i.e., floating microspheres will be possibly beneficial for sustained action.

When it is formulated in large scale, the formulation will be economical, due to its ease of preparation and buoyancy due to the polymers used in the formulation. Thus, the prepared formulation may reduce the frequency of dosing, thereby minimizing occurrence of side effects, increase residence time in stomach and increase the effectiveness of the drug.

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